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Description

[0001] The present invention relates to a chemical compound. In particular the present invention relates to a chemical compound suitable for use as an anti-viral agent. The present invention also relates to the therapeutic use of the present chemical compound, to a pharmaceutical composition containing the present compound and to use of the present compound in the manufacture of a medicament.

[0002] Since the recognition of human acquired immunodeficiency syndrome (AIDS) much interest and research activity has been directed to its understanding and to attempting to provide a means of treatment. The human immunodeficiency virus (HIV) has been identified as the presumed aetological agent in AIDS. A large literature now exists related to the use of a wide variety of chemical compounds having as their object a demonstration of anti-viral activity with respect to HIV, hepatitus B virus (HBV), herpes and other viruses.

[0003] A class of compounds which has demonstrated anti-viral activity and which has been the subject of a large amount of research are nucleoside analogues.

[0004] An example of such a compound is "Abacavir" which is a substituted adenine analogue (Foster R.H. & Faulds D. Drugs 1998 55 729-736). This compound has entered clinical use due to the potential activity and stability of the compound displayed in preliminary work.

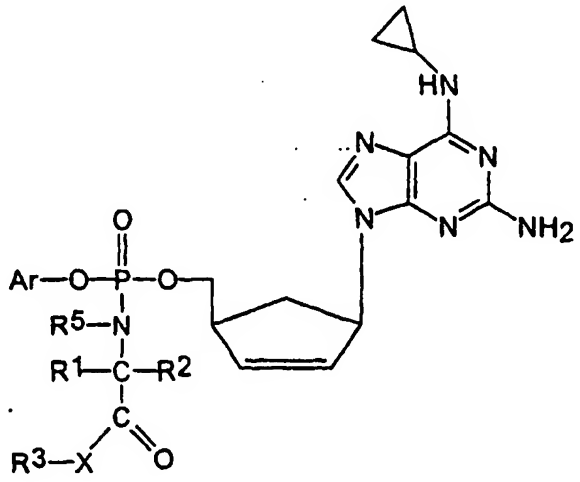
[0005] WO-9629336 relates to a class of nucleoside analogues said to be highly active with respect to HIV. In particular WO-9629336 addresses the problem of providing compounds which are said to be highly potent *in vitro* viral inhibitors in both TK^- and TK^+ cells. The compounds disclosed in WO-9629336 are phosphoramidates of purine or pyrimidine nucleoside analogues. Such compounds can however display chemical, for example acid, or biological, for example nucleoside phosphorylase, instability towards glycoside bond cleavage. Consequential deactivation may limit their potential clinical efficacy.

[0006] A compound however to be potentially useful in a clinical setting needs to exhibit a number of other properties as well as demonstrating, at least In *in vitro* tests, a sufficient and desired anti-viral activity. Primarily, these other properties comprise good pharmacokinetic properties, sufficient stability in the compound to permit its ease of handling and supply, and sufficiently low toxicity to permit its administration with an acceptable level of side effects to a patient in need of treatment for the viral infection in question.

[0007] In practice however it is frequently found that attempts to modify a compound demonstrating anti-viral activity *in vitro*, in order to improve its other properties, can have a detrimental effect on the anti-viral activity it displays. Ideally moreover any compound proposed for clinical trials needs also to have a ready means of administration and to be prepareable by an economically viable route.

[0008] It is an object of the present invention to provide a novel class of compounds exhibiting potent anti-viral, in particular anti HIV and/or HBV activity, in combination with good pharmacokinetic and stability properties and exhibiting sufficiently low toxicity so as to provide a compound having beneficial properties for clinical use.

[0009] According to the present invention there is provided a compound according to the following formula (I):



wherein
Ar is an aryl group,

R^1 and R^2 are independently selected from the group comprising H, alkyl and aryl groups;
X is selected from the group comprising O, NH, NR^4 and S wherein R^4 is selected from the group comprising alkyl and aryl groups;
R^5 is selected from the group comprising H, alkyl and aryl groups, wherein when R^1 and R^5 are each alkyl they may be linked to form a 5- or 6- membered ring;
and R^3 is selected from the group comprising H, alkyl, aryl, heterocyclic and polycyclic groups,
or a pharmaceutically acceptable derivative or metabolite thereof.

[0010] The present invention includes salts and physiologically functional derivatives of the presently defined compounds.

[0011] Reference in the present specification to an alkyl group means a branched or unbranched, cyclic or acyclic, saturated or unsaturated (e.g. alkenyl or alkynyl) hydrocarbyl radical. Where cyclic, the alkyl group is preferably C_3 to C_{12}, more preferably C_5 to C_{10}, more preferably C_5 to C_7. Where acyclic, the alkyl group is preferably C_1 to C_{16}, more preferably C_1 to C_6, more preferably methyl or ethyl.

[0012] Reference in the present specification to an aryl group means an aromatic group, such as phenyl or naphthyl, or a heteroaromatic group containing one or more, preferably one, heteroatom for example O, N and/or S, such as pyridyl, pyrrolyl, furanyl and thiophenyl. Preferably, the aryl group comprises phenyl or substituted phenyl.

[0013] The alkyl and aryl groups may be substituted or unsubstituted, preferably unsubstituted. Where substituted, there will generally be 1 to 3 substituents present, preferably 1 substituent. Substituents may include halogen atoms and halomethyl groups such as CF_3 and CCl_3; oxygen containing groups such as oxo, hydroxy, carboxy, carboxyalkyl, alkoxy, alkoyl, alkoyloxy, aryloxy, aryloyl and aryloyloxy; nitrogen containing groups such as amino, alkylamino, dialkylamino, cyano, azide and nitro; sulphur containing groups such as thiol, alkylthiol, sulphonyl and sulphoxide, heterocyclic groups which may themselves be substituted; alkyl groups, which may themselves be substituted; and aryl groups, which may themselves be substituted, such as phenyl and substituted phenyl. Alkyl includes substituted and unsubstituted benzyl. Reference in the present specification to alkoxy and aryloxy groups means alkyl-O- and aryl-O- groups, respectively. Reference to alkoyl and aryloyl groups means alkyl-CO- and aryl-CO-, respectively.

[0014] Reference in the present specification to heterocyclic groups means groups containing one or more, optionally bridged, rings containing 1 to 6 heteroatoms in total. Each ring in the group may contain 3 to 12, preferably 1 to 6, atoms in total. At least one ring present contains 1 to 2 heteroatoms. Where two or more rings are present they may be fused or unfused. The rings can contain unsaturation. Heteroatoms includes O, S and N. Examples of such heterocyclic groups containing one or more pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, piperidyl, piperazinyl, morpholinyl, thionaphthyl, benzofuranyl, isobenzofuryl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, isoindazolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolyl, isoquinolyl, napthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxadinyl, chromenyl, chromanyl, isochromanyl and carbolinyl.

[0015] References in the present specification to polycyclic groups means a group comprising two or more non-aromatic carbocyclic or heterocyclic rings which may themselves be substituted. Preferably the group contains 2 to 4 fused or non-fused rings, each ring suitably containing 3 to 12 atoms, more suitably 4 to 10, more suitably 5 to 7, and even more suitably 5 to 6 atoms. The definitions of cyclic alkyl and heterocyclic rings given above also apply to the rings in the polycyclic groups.

[0016] Reference in the present specification to halogen means a fluorine, chlorine, bromine or iodine radical, preferably fluorine or chlorine radical.

[0017] The group Ar comprises a substituted or unsubstituted aryl group, wherein the term "aryl group" and the possible substitution of said group is as defined above. Preferably, Ar is a substituted or unsubstituted phenyl group. Particularly preferred substituents are electron withdrawing groups such as halogen (preferably chlorine or fluorine), trihalomethyl (preferably trifluoromethyl), cyano and nitro groups. Preferably, Ar is phenyl, 3,5-dichloro-phenyl, p-trifluoromethyl-phenyl, p-cyano-phenyl, or p-nitro-phenyl.

[0018] R^3 is selected from hydrogen, alkyl, aryl, heterocyclic and polycyclic groups.

[0019] Preferably, R^3 is a substituted or unsubstituted alkyl group. Preferably, R^3 is a substituted or unsubstituted C_{1-6} alkyl group, more preferably an ethyl or methyl group.

[0020] Preferably, R^3 is selected from the group comprising $-CH_3$, $-C_2H_5$ and $-CH_2Ph$.

[0021] Preferably, at least one of R^1 and R^2 is hydrogen. It will be appreciated that if R^1 and R^2 are different, the carbon atom to which they are bonded is an asymmetric centre.

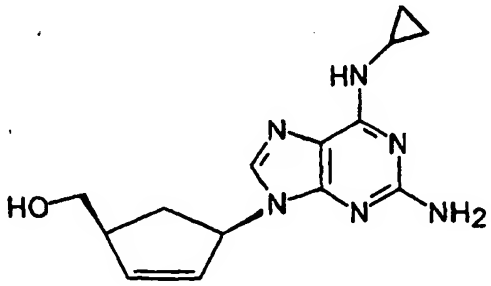
[0022] Preferably this carbon atom is chiral. When this carbon atom is chiral, the stereochemistry at this site may be D or L or mixed, with L-stereochemistry being preferred.

[0023] Suitably, R^1 and R^2 are the same or different and are H, $-CH_3$ or $-C_2H_5$. Preferably, R^1 is H and R^2 is $-CH_3$, $-CH_2CH_3$ or CH_2Ph.

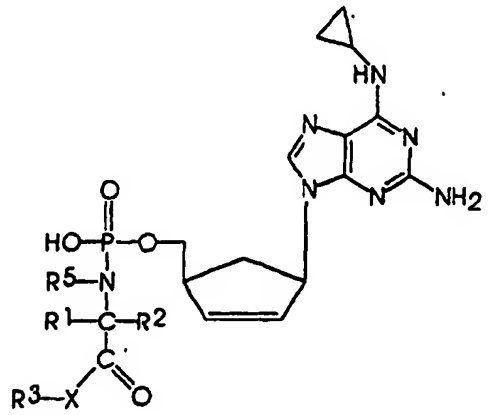
[0024] R^5 and R^1 can be linked to form an alkylene bridge comprising 3 to 4 carbon atoms so as to form a 5- or 6-membered ring. Preferably R^5 is hydrogen.

[0025] It will be appreciated that the group -NH-CHR^1-CO_2R^3 corresponds to a carboxy-protected α-amino acid. Preferably, the group R^1 corresponds to the side chain of a naturally occurring amino acid such as Alanine, Arginine, Asparagine, Aspartic Acid, Cysteine, Cystine, Glycine, Glutamic Acid, Glutamine, Histidine, Isoleucine, Leucine, Lysine, Methionine, Phenylalanine, Proline, Serine, Threonine, Tryptophan, Tyrosine, Valine. Preferably, R^1 is Me or $PhCH_2$ corresponding to the side chain of alanine or phenylalanine, respectively. Preferably, the stereochemistry at the asymmetric centre -CHR^1- corresponds to an L-amino acid.

[0026] It is a feature of the aryl ester phosphate compounds of the present invention that they exhibit significantly enhanced anti-viral efficacy in *in vitro* tests, in comparison to their corresponding nucleoside analogue, (1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol, which is known as Abacavir and which has the following structural formula:



[0027] According to a further aspect of the present invention there is provided a compound of formula (II):



wherein R^1, R^2, R^3, R^5 and X are as defined above, or a pharmaceutically acceptable derivative or metabolite thereof. Preferably X is O.

[0028] The intracellular generation of such anti-viral metabolites is an important feature of the invention for several reasons. In cases where the nucleoside is not a good substrate for host nucleotide kinases, activation will be poor and anti-viral efficacy low, even if the triphosphate is an excellent RT inhibitor. In such cases, the generation of the present metabolites may lead to a very significant enhancement in anti-viral action.

[0029] By "a pharmaceutically acceptable derivatives" is meant any pharmaceutically acceptable salt, ester or salt of such ester or any other compound which upon administration to a recipient is capable of providing (directly or indirectly) a compound of the present formula or present metabolite. Preferred "pharmaceutically acceptable derivatives" include sodium, succinate, fumarate, glutarate and D-tartrate salts.

[0030] By "pharmaceutically acceptable metabolite" is meant a metabolite or residue of a compound of the present formula or present metabolite which gives rise to reverse transcriptase inhibition exhibited by the present compounds.

[0031] According to a further aspect of the present invention there is provided a compound according to the present

invention for use in a method of treatment, prophylaxis or diagnosis, preferably in the prophylaxis or treatment of viral infection.

[0032] According to a further aspect of the present invention there is provided use of a compound according to the present invention in the manufacture of a medicament for the prophylaxis or treatment of viral infection.

[0033] A method of prophylaxis or treatment of viral infection can comprise administration to a patient in need of such treatment an effective dose of a compound according to the present invention.

[0034] The viral infection may comprise any viral infection such as HIV and herpes virus, including HSV 1 and HSV 2, CMV, VZV, EBV, HAV, HBV, HCV, HDV, HHV6, HHV7, HHV8, papilloma, adenoviruses, rabies and influenza.

[0035] Preferably, the viral infection comprises HIV or HBV infection, more preferably HIV-I or HIV-II. It is a feature of the present invention that the compounds exhibit good activity against HIV-I and HIV-II, and HBV.

[0036] According to a further aspect of the present invention there is provided a pharmaceutical composition comprising a compound of the present invention in combination with a pharmaceutically acceptable excipient.

[0037] According to a further aspect of the present invention there is provided a method of preparing a pharmaceutical composition comprising the step of combining a compound of the present invention with a pharmaceutically acceptable excipient.

[0038] Compounds of the present invention can demonstrate significant stability towards acid-mediated hydrolytic decomposition. The present compounds can thus be particularly suitable for oral administration under typical dosing conditions in humans as they can retain stability under the highly acidic environment of the stomach.

[0039] As the purine in compounds of formula (I) is a weak base (pKa=5.0) and the compounds of formula (I) demonstrate stability to acids, salts can be formed of compounds of formula (I) with acids, such as carboxlic acids and dicarboxlic acids. Such salts can be stable, crstalline solids, which can be beneficial in terms of improved shelf-life and ease of handling during manufacture into pharmaceutical compositions. Preferred carboxylic and dicarboxylic acids include malonic, succinic, glutaric, fumaric and tartaric acids. In contrast to the salts of compounds of formula (I), the free bases of compounds of formula (I) can be in a non-crystalline amorphous form which can be hygroscopic.

[0040] The P-OH group of compounds of formula (II) is a weak acid and can therefore form monobasic salts with bases to give, for example, sodium, potassium, ammonium, and triethylammonium salts. In compounds of formula (II) when X is OH, dibasic salts can be formed. Such dibasic salts can be in the form of stable solids, which can provide benefits of improved shelf-life and ease of handling during manufacture into pharmaceutical compositions.

[0041] Compounds of the present invention can also demonstrate enhanced stability in biological media, for example, in human plasma. The increased half-life of compounds embodying the present invention in media such as human plasma may permit a pharamacokinetic advantage in dosing in humans in need of treatment.

[0042] The medicament employed in the present invention can be administered by oral or parenteral routes, including intravenous, intramuscular, intraperitoneal, subcutaneous, transdermal, airway (aerosol), rectal, vaginal and topical (including buccal and sublingual) administration.

[0043] For oral administration, the compounds of the invention will generally be provided in the form of tablets or capsules, as a powder or granules, or as an aqueous solution or suspension.

[0044] Tablets for oral use may include the active ingredients mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavouring agents, colouring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose, while corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin, while the lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract.

[0045] Capsules for oral use include hard gelatin capsules in which the active ingredient is mixed with a solid diluent, and soft gelatin capsules wherein the active ingredients is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

[0046] Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

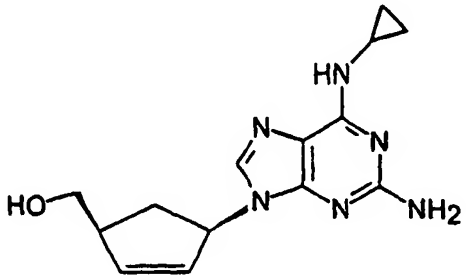
[0047] Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

[0048] For intramuscular, intraperitoneal, subcutaneous and intravenous use, the compounds of the invention will generally be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride. Aqueous suspensions according to the invention may include suspending agents such as cellulose derivatives, sodium alginate, polyvinylpyrrolidone and gum tragacanth, and a wetting agent such as lecithin. Suitable preservatives for aqueous suspensions include ethyl and n-propyl p-hydroxybenzoate.

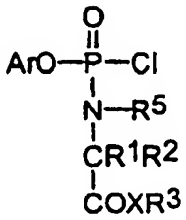
[0049] The compounds of the invention may also be presented as liposome formulations.

[0050] In general a suitable dose will be in the range of 0.01 to 10 mg per kilogram body weight of the recipient per day, preferably in the range of 0.2 to 1.0 mg per kilogram body weight per day. The desired dose is preferably presented once daily, but may be dosed as two, three, four, five or six or more sub-doses administered at appropriate intervals throughout the day. These sub-doses may be administered in unit dosage forms, for example, containing 10 to 1500 mg, preferably 20 to 1000 mg, and most preferably 50 to 700 mg of active ingredient per unit dosage form.

[0051] According to a further aspect of the present invention there is provided a process for the preparation of the present compound comprising reaction of a compound of formula



with a compound of formula



wherein R^1, R^2, R^3, R^5 and X have the meanings given above.

[0052] The reaction may be carried out under dry conditions at ambient temperature in tetrahydrofuran in the presence of N-methylimidazole, or by using t-butyl magnesium chloride and an excess of the appropriate phosphorochlorideate reagent.

[0053] Compounds embodying the present invention wherein Ar is replaced by H may be prepared from the acid form by treatment of the ester with an aqueous base.

[0054] Compounds wherein X is NH or NR^4 can be prepared by treating the acid form (X = O and R^3 = H) with amine.

[0055] The above starting material, (1S, 4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol, is known as Abacavir and may be made by any procedure known in the art, for example by procedures described in European Patent Specification Number 0434450, PCT Patent Application No. PCT/GB95/02014, and PCT Patent Application No. PCT/EP98/02835.

[0056] The invention will now be described with reference to the following Examples. It will be appreciated that what follows is by way of example only and that modifications to detail may be made whilst still falling within the scope of the invention.

EXPERIMENTAL PROCEDURES

General methods

[0057] The following anhydrous solvents and reagents were bought dry from Aldrich with sure seal stoppers: Dichloromethane (DCM), diethyl ether (Et_2O), tetrahydrofuran (THF), N-methyl imidazole (NMI), methanol (MeOH), dimethylformamide (DMF), pyridine (pyr), dioxane, and tBuMgCl. Triethylamine (NEt_3) was dried by refluxing over CaH_2 for several hours and then distilled off for immediate use.

Chromatography

[0058] Thin layer chromatography (tlc) was performed on commercially available Merck Kieselgel 60F_{254} (product name) plates and the separated components were visualised using ultra violet light (254nm and 366nm), or by treatment with a 5% ethanolic solution of dodeca-molybdo-phosphoric acid (MPA) followed by heating. Column chromatography was performed using Woelm silica (32-63mm) as the stationary phase.

Spectral Characterisation

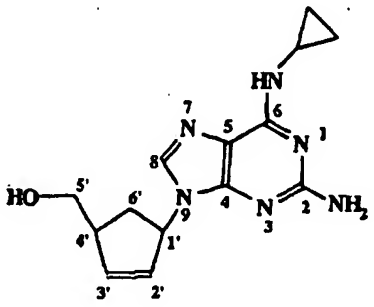
[0059] All NMR spectral data, unless otherwise stated, were obtained in $CDCl_3$. Proton and Carbon-13 nuclear magnetic resonance were recorded on a Bruker Avance DPX300 (product name) spectrometer with operating frequencies of 300MHz and 75MHz respectively. Phosphorous-31 NMR spectra were recorded on a Bruker Avance DPX300 spectrometer operating at 121MHz, and are reported in units of δ relative to 85% phosphoric acid as the external standard, positive shifts are downfield. The following abbreviations are used in the assignment of NMR signals: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), bs (broad signal), dd (double of doublets), dt (double of triplets).

[0060] Low resolution mass spectra were run on a VG Platform II Fisons instrument (Fisons, Altrincham, UK) (atmospheric pressure ionization, electrospray mass spectrometry) in either negative or positive ion mode.

[0061] High Performance Liquid Chromatography (HPLC) was performed on an SSODS2 (product name) reverse phase column with an eluent of water/acetonitrile. 100% water (0 mins), 20% water (35mins), 20% water (45mins), 100% water (55mins), with a flow rate of 1 ml/min and detection by UV at 254 nm. Standards: acetone (t_R 4.54mins), toluene (t_R 10.21mins). Final products showed purities >99%, with undetectable amounts of the parent nucleoside.

Nomenclature and Numbering of Compounds

[0062] IUPAC nomenclature is used where possible, but for ease some compounds are abbreviated. Numbering is by conventional nucleoside numbering.



Standard Procedures

[0063] For practical purposes, standard procedures are given where applicable.

Standard Procedure 1

[0064] To a stirring solution of anhydrous alcohol (10mol eq) was added thionyl chloride (2mol eq) dropwise at 0°C, and the resulting solution stirred for 1hr. Upon rising to room temperature, the appropriate amino acid (1mol eq) was added and the reaction heated at reflux for 6-16hrs. Removal of the solvent and recrystallisation from methanol:ether gave the amino ester hydrochloride salts.

Standard Procedure 2

[0065] The appropriate amino acid (1mol eq), *p*ara-toluene sulfonic acid (1.1mol eq) and the appropriate alcohol (1mol eq) were heated under reflux in toluene (100ml), under Dean and Stark conditions, for 6-16hrs. On cooling to room temperature the solvent was removed under reduced pressure to give an oil. This was solubilised in dichloromethane (50ml) and washed with 10% K_2CO_3 (50ml), and water (50ml), filtered and the filtrate reduced to dryness to give

an oil. This was solubilised in the minimum amount of acetone and neutralised with 2M HCl, and then lyophilised to give the amino acid ester hydrochloride salts.

Standard procedure 3

[0066] Phenyl dichlorophosphate (lmol eq) and the appropriate amino acid ester hydrochloride salt (1mol eq) were suspended in anhydrous dichloromethane (30-60ml). Anhydrous triethylamine (2mol eq) in anhydrous dichloromethane (30ml) was added dropwise at-80°C, and the reaction left to rise to room temperature overnight. The solvent was removed under reduced pressure, and under nitrogen, to give white solids. This was washed with anhydrous ether (2x25ml), filtered and the filtrate reduced to dryness to give the products as crude oils. These were stored in anhydrous THF and used without any further purification.

Standard Procedure 4

[0067] (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (1mol eq) was dried by azeotroping with anhydrous pyridine (3x5ml), and then suspended in anhydrous THF (5-30ml). To the suspension was added tBuMgCl (1-2mol eq, 1.0M solution in THF) dropwise, and the resulting suspension stirred for 10mins. The phosphorochloridate species (3mol eq, solution in THF) was then added dropwise and the resulting solution stirred at room temperature for 24-96hrs. The reaction was then quenched by the addition of sat.NH_4Cl (0.1ml), and after 10mins the solvent was removed under reduced pressure. The crude product was purified by silica column chromatography.

L-Alanine methyl ester hydrochloride.

$C_4H_{10}O_2N_1Cl_1$, MW=139.38.

[0068] This was synthesised according to **Standard Procedure 1,** using anhydrous methanol (34ml, 0.84mol), thionyl chloride (8.2ml, 0.112mol) and L-alanine (5.0g, 0.056mol). The product was isolated as a white solid (2.87g, 36.7%).
^1H NMR (D_2O): δ 4.07-4.00 (1H,q,CH,J=7.22Hz), 3.83 (3H,s,OCH_3), 1.39-1.37 (3H,t,CH_3).
^{13}C NMR (D_2O): δ 171.5 (CO), 53.9 (O CH_3), 49.1 (CH), 15.4 (CH_3).

Phenyl-(methoxy-L-alaninyl)-phosphorochloridate.

$C_{10}H_{13}O_4N_1Cl_1P_1$, MW=277.65.

[0069] This was synthesised according to **Standard Procedure 3,** using L-Alanine methyl ester hydrochloride (2.0g, 14.34mmol), phenyl phosphorodichloridate (3.02g, 2.14ml, 14.34mmol) and anhydrous triethylamine (2.90g, 4.0ml, 28.68mmol). The product (3.91g, 98.2%) was isolated as a colourless crude oil which was stored in anhydrous THF (40ml) to give a 0.47M solution.
^{31}P NMR: δ 9.28, 8.97 (1:1).
^1H NMR: δ 7.39-7.34 (2H,m,'*o*'-Ph), 7.29-7.20 (3H,m,'*m*'+'*p*'-Ph), 4.49-4.37 (1H,q,NHala), 4.27-4.09 (1H,m,CHala), 3.78 (3H,d,OCH_3), 1.52-1.49 (3H,dd,CH_3).
^{13}C NMR: 173.6 (CO), 150.1 ('*ipso*'-Ph), 130.25 ('*m*'-Ph), 126.4 ('*p*'-Ph), 120.9 ('*o*'-Ph), 53.2 (OCH_3), 51.0 (CH), 20.9 (CH_3ala).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl-(methoxy-L-alaninyl)]-phosphate. Cf1490.

$C_{24}H_{30}O_5N_7P_1$, MW=527.53.

[0070] This was synthesised according to **Standard Procedure 4,** using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (500mg, 1.75mmol), tBuMgCl (1.0M solution in THF) (1.75ml, 1.75mmol) and phenyl-(methoxy-L-alaninyl)-phosphorochloridate (0.47M solution in THE) (11.17ml, 5.24mmol), in THF (30ml) and stirring at room temperature for 70hrs. The crude product was purified by column chromatography eluting with 3% MeOH in DCM and then 2% MeOH in DCM to give the product as a white foam (442mg, 48%).
^{31}P NMR (MeOH-d_4): δ 3.97, 3.88.
^1H NMR: δ 7.41 (1H,d,C8), 7.24-7.19 (2H,m,'*o*'-Ph), 7.13-7.03 (3H,m,'*m*'+'*p*'-Ph), 6.08 (1H,bs,NH), 5.98 (1H,q,H2'), 5.78 (t,H3'), 5.44 (1H,t,H1'), 5.09 (2H,bs,NH_2), 4.22-4.02 (3H,m,NHala+H5'), 3.99-3.87 (1H,m,CHala), 3.59 (3H,t, OCH_3), 3.05 (1H,d,H4'), 2.92 (1H,bs,CHcPr), 2.73-2.62 (1H,m,1of H6'), 1.62-1.53 (1H,m,lof H6'), 1.30-1.25 (3H,t,

CH_3ala), 0.78-0.71 (2H,q,2H of CH_2cPr), 0.54-0.49 (2H,t,2H of CH_2cPr).
^{13}C NMR: δ 174.6 (CO), 160.3 (C2), 156.6 (C4), 151.3 (C6), 151.1 ('*ipso*'-Ph), 136.8 (C8), 135.9 (C2'), 131.5 (C3'), 130.0 ('*m*'-Ph), 125.2 ('*p*'-Ph), 120.5 ('*o*'-Ph), 115.0 (C5), 69.2 (C5'), 59.2 (C1'), 52.8 (OCH_3), 50.5 (CHala), 46.0 (C4'), 34.9 (C6'), 24.2 (CHcPr), 21.2 (CH_3ala), 7.7 (CH_2cPr).
MS ES$^+$: m/z 527.86 (100%) $(M)^+$, 546.84 $(M+K)^+$.
MS FAB: For $C_{24}H_{31}O_5N_7P$, requires 528.212431, found 528.213848.
HPLC: t_R 30.33 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).
IR: 3328.6 (N-Hstr.), 2922.1, 2862.9 (C-Hstr.), 1734.4 (C=Ostr.), 1590.9 (aromatic C-Cstr.), 1462.9 (C-Hdef.), 1376.8 (-CH_3sym.def.), 1207.1 (P-O-aryl), 1154.0 (C-Ostr.), 1027.7 (P-O-alkyl), 933.4 (olefinic C-Hdef.), 721.8 (monosub. aromatic C-Hdef).

Phenyl-(methoxy-D-alaninyl)-phosphorochloridate.

$C_{10}H_{13}O_4N_1Cl_1P_1$, MW=277.65.

[0071] This was synthesised according to **Standard Procedure 3,** using D-alanine methyl ester hydrochloride (1.0g, 7.17mmol), $PhOP(O)Cl_2$ (1.51g, 1.07ml, 7.17mmol) and NEt_3 (1.45g, 2.0ml, 14.0mmol) to yield 1.66g (83.4%) of crude product that was stored in anhydrous THF (10ml), to give a 0.60mmol/ml solution that was used without further purification.
^{31}P NMR: δ 9.38, 9.18 (1:1).
^{1}H NMR: δ 7.39-7.30 (2H,t,'*o*'-Ph), 7.29-7.09 (3H,m,'*m*'+'*p*'-Ph), 4.85-4.80 (1H,d,NHala), 4.19-4.11 (1H,m,CHala), 3.75 (3H,d,OCH_3), 1.52-1.49 (3H,dd,CH_3ala).
^{13}C NMR: δ 173.6 (CO), 150.1 ('*ipso*'-Ph), 130.3 ('*o*'-Ph), 126.4 ('*p*'-Ph), 120.9 ('*m*'-Ph), 53.2 (OCH_3), 50.9 (CHala), 21.0 (CH_3ala).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl-(methoxy-D-alaninyl)]-phosphate. Cf1583.

$C_{24}H_{30}O_5N_7P_1$, MW=527.53.

[0072] This was synthesised according to **Standard Procedure 4**, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (400mg, 1.4mmol), tBuMgCl (1.0M solution in THF) (2.1ml, 2.1mmol), and phenyl-(methoxy-D-alaninyl)-phosphorochloridate (0.6M solution in THF) (7.0ml, 4.19mmol) in THF (25ml) stirring at room temperature for 36hrs. The crude product was purified by eluting with 3% MeOH in $CHCl_3$ and then 2.5% MeOH in $CHCl_3$ to give the product as a white foam (318.6mg, 43.2%).
^{31}P NMR: δ 3.93, 3.70.
^{1}H NMR: δ 7.56+7.51 (1H,d,H8), 7.37-7.32 (2H,m,'*o*'-Ph), 7.29 (1H,d,'*p*'-Ph), 7.25-7.15 (2H,m,'*m*'-Ph), 6.10 (1H,t, J=5.28Hz,H2'), 6.03 (1H,bs,NHcPr), 5.94-5.89 (1H,m,H3'), 5.54 (1H,bs,H1'), 5.01 (2H,bs,NH_2), 4.26-3.83 (4H,m,CHa-la,NHala+H5'), 3.72 (3H,d,OCH_3), 3.18 (1H,s,CHcPr), 3.02 (1H,bs,H4'), 2.86-2.75 (1H,m,1 of H6'), 1.78-1.64 (1H,m, 1 of H6'), 1.39-1.36 (3H,dd,CH_3ala), 0.90-0.83 (2H,q,J=6.13Hz,2H of CH_2cPr), 0.63 (2H,bs, 2H of CH_2cPr).
^{13}C NMR: δ 174.5 (CO), 160.3 (C2), 156.6 (C4) 151.2 (C6), 151.0 ('*ipso*'-Ph), 136.8 (C2'), 136.1 (C8), 131.5 (C3'), 130.0 ('*m*'-Ph), 125.3 ('*p*'-Ph), 120.5 ('*o*'-Ph), 115.2 (C5), 69.3 (C5'), 59.3 (C1'), 52.9 (CHala), 50.5 (OCH_3), 46.0 (C4'), 34.9 (C6'), 24.1 (CHcPr), 21.4 (CH_3ala), 7.8 (CH_2cPr).
MS ES$^+$: m/z 527.86 (100%) $(M)^+$, 546.84 $(M+K)^+$.
MS FAB: For $C_{24}H_{31}O_5N_7P$ requires 528.212431, found 528.211505.
HPLC: t_R 29.807 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).
IR: 3333.6 (N-Hstr.), 2923.4, 2853.4 (C-Hstr.), 1734.1 (C=Ostr.), 1591.1 (aromatic C-Cstr.), 1458.3 (C-Hdef.), 1376.7 (-CH_3sym.def.), 1208.3 (P-O-aryl), 1153.3 (C-Ostr.), 1026.9 (P-O-alkyl), 931.9 (olefinic C-Hdef.), 721.6 (monosub. aromatic C-Hdef.).

Phenyl-(methoxy-L-phenylalaninyl)-phosphorochloridate.

$C_{16}H_{17}O_4N_1Cl_1P_1$, MW=353.74.

[0073] This was synthesised according to **Standard Procedure 3,** using L-phenylalanine methyl ester (1.0g, 4.64mmol), $PhOP(O)Cl_2$ (0.98g, 0.70ml, 4.64mmol) and NEt_3 (0.94g, 1.30ml, 9.28mmol) to yield 1.45g (88.4%) of crude product as an oil that was stored in anhydrous THF (10ml), to give a 0.41mmol/ml solution that was used without further purification.

^{31}P NMR: δ 9.37, 9.23 (1:1).
^{1}H NMR: δ 7.60-7.16 (10H,m,2xPh), 4.70-4.49 (1H,m,CHala), 4.38-4.16 (1H,m,NHala), 3.89 (3H,d,OCH_3), 3.23 (2H, m,$\underline{CH_2}$Ph).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl-(methoxy-L-phenylalaninyl)]-phosphate. Cf1585.

$C_{31}H_{34}O_5N_7P_1$, MW=603.6.

[0074] This was synthesised according to **Standard Procedure 4,** using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (300mg, 1.05mmol), tBuMgCl (1.0M solution in THF) (1.57ml, 1.57mmol) and phenyl-(methoxy-L-phenylalaninyl)-phosphorochloridate (0.41M solution in THF) (7.66ml, 3.14mmol) in THF (20ml) stirring at room temperature for 48hrs. The crude product was purified by eluting with 3% MeOH in $CHCl_3$ and then 2.5% MeOH in $CHCl_3$ to give the product as a white foam (272.9mg, 43.15%).
^{31}P NMR: δ 3.91, 3.80.
^{1}H NMR: δ 7.47+7.43 (1H,d,H8), 7.31-7.06 (10H,m,2xPh), 6.25 (1H,d,NHcPr), 6.00-5.95 (1H,q,H2'), 5.87-5.81 (1H,t, H3'), 5.49 (1H,s,H1'), 5.19 (2H,bs,NH_2), 4.31-3.92 (4H,m,CHala,NHala+H5'), 3.64 (3H,d,OCH_3), 3.02-2.89 (4H,m, $\underline{CH_2}$Ph,CHcPr+H4'), 2.78-2.63 (1H,m,1 of H6'), 1.63-1.49 (1H,m,1 of H6'), 0.86-0.80 (2H,q,J=6.24Hz,2H of CH_2cPr), 0.60 (2H,d,2H of CH_2cPr).
^{13}C NMR: δ 174.3 (CO), 161.5 (C2), 157.7 (C4), 152.4 (C6) 152.1 ('*ipso*'-OPh), 137.7 ('*ipso*'-Bn), 137.1 (C2'), 136.9 (C8), 132.4 (C3'), 130.9 ('*o*'+'*m*'-Bn), 129.9 ('*m*'-OPh), 128.4 ('*p*'-Bn), 126.2 ('*p*'-OPh), 121.5 ('*o*'-OPh), 116.1 (C5), 70.1 (C5'), 60.1 (C1'), 57.2 (CHala), 53.6 (OCH_3), 46.9 (C6'), 41.7 (C4'), 35.9 ($\underline{C}H_2$Ph), 25.1 (CHcPr), 8.7 (CH_2cPr).
MS ES$^+$: m/z 603.8 (100%, M^+), 604.8 (35%, $M+H^+$), 625.7 (15%, $M+Na^+$).
MS FAB: For $C_{31}H_{34}O_5N_7P$ requires 604.243731, found 604.242585.
HPLC: t_R 34.707, 35.020 (100%)-(100% water (0mins) 20% water (35mins), 20% water (45mins), 100% water (55mins)).
IR: 3331.7 (N-Hstr.), 3007.2, 2952.2 (C-Hstr.), 1741.1 (C=Ostr.), 1595.6, 1487.7 (aromatic C-Cstr.), 1455.0 (C-Hdef.), 1393.9 (-CH_3sym.def.), 1252.5 (P=O), 1214.3 (P-O-aryl), 1125.3 (C-Ostr.), 1025.6 (P-O-alkyl), 935.8 (olefinic C-Hdef.), 754.8 (monosub.aromatic C-Hdef.).

Pbenyl-(methoxyglycinyl)-phosphorochloridate.

$C_9H_{11}O_4N_1Cl_1P_1$, MW=263.62.

[0075] This was synthesised according to **Standard Procedure** 3, using glycine methyl ester (1.5g, 11.9mmol), $PhOP(O)Cl_2$ (2.52g, 1.79ml, 11.9mmol) and NEt_3 (2.42g, 3.33ml, 23.9mmol) to yield 3.07g (97.15%) of crude product as an oil that was stored in anhydrous THF (15ml), to give a 0.774mmol/ml solution that was used without further purification.
^{31}P NMR: δ 10.43.
^{1}H NMR: δ 7.43-7.38 (2H,m,'*o*'-Ph), 7.31-7.25 (3H,m,'*m*'+'*p*'-Ph), 4.67 (1H,bs,NHala), 3.94 (2H,dd,CH_2), 3.83 (3H,s, OCH_3).
^{13}C NMR: δ 170.4 (CO), 150.1 ('*ipso*'-Ph), 130.2 ('*m*'-Ph), 126.4 ('*p*'-Ph), 120.8 ('*o*'-Ph), 53.1 (OCH_3), 43.4 (CH_2).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl-(methoxy-glycinyl)]-phosphate. Cf1588.

$C_{23}H_{28}O_5N_7P_1$, MW=513.49.

[0076] This was synthesised according to **Standard Procedure 4,** using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (300mg, 1.05mmol), tBuMgCl (1.0M solution in THF) (1.57ml, 1.57mmol) and phenyl-(methoxy-glycinyl)-phosphorochloridate (0.774M solution in THF) (4.06ml, 3.14mmol) in THF (20ml) stirring at room temperature for 96hrs. The crude product was purified by eluting with 3% MeOH in $CHCl_3$ and then with 2.5% MeOH in $CHCl_3$ to give the product as a white foam (82.6mg, 15.4%).
^{31}P NMR: δ 4.79, 4.67 (1:1).
^{1}H NMR: δ 7.40+7.36 (1H,d,H8), 7.24-7.19 (2H,t,'*o*'-Ph), 7.15-7.10 (2H,t,'*m*'-Ph), 7.07-7.02 (1H,t,'*p*'-Ph), 6.00-5.96 (2H, m,H2'+NHcPr), 5.80-5.76 (1H,m,H3'), 5.45-5.41 (1H,t,H1'), 4.99 (2H,bs,NH_2), 4.14-4.00 (3H,m,NHala+H5'), 3.62 (3H, s,OCH_3), 3.03 (1H,d,H4'), 2.91 (1H,d,CHcPr), 2.73-2.62 (1H,m,1 of H6'), 1.62-1.51 (1H,m,1 of H6'), 1.45-1.43 (6H,t, 2xCH_3), 0.78-0.71 (2H,q,2H of CH_2cPr), 0.54-0.49 (2H,t,2H of CH_2cPr).

^{13}C NMR: δ 172.1 (CO), 160.2 (C2), 156.6 (C4), 152.0 (C6), 151.7 ('*ipso*'-Ph), 137.7 (C8), 137.1 (C2'), 132.0 (C3'), 130.8 ('*m*'-Ph), 126.0 ('*p*'-Ph), 121.2 ('*o*'-Ph), 115.5 (C5), 69.9 (C5'), 60.0 (C1'), 53.5 (OCH_3), 46.7 (C4'), 43.9 (CH_2), 35.4 (C6'), 25.0 (CHcPr), 8.5 (CH_2cPr).
MS ES$^+$: m/z 513.9 (100%, M$^+$), 514.8 (25%, M+H$^+$), 535.8 (40%, M+Na$^+$).
MS FAB: For $C_{23}H_{29}O_5N_7P$ requires 514.196781, found 514.195321.
HPLC: t_R 28.419 (99.9%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).
IR: 3342.0 (N-Hstr.), 1749.8 (C=Ostr.), 1596.2, 1488.4 (aromatic C-Cstr.), 1451.9 (C-Hdef.), 1394.7 (-CH_3sym.def.), 1259.6 (P=O), 1212.1 (P-O-aryl), 1151.6 (C-Ostr.), 1026.8 (P-O-alkyl), 937.8 (olefinic C-Hdef.), 760.7 (monosub.aromatic C-Hdef.).

Methyl-2-amino-2-methylpropanoate hydrochloride.

$C_5H_{12}O_2N_1Cl_1$, MW=153.61.

[0077] This was synthesised according to **Standard Procedure 1,** using 2-amino-isobutyric acid (4g, 0.039mol) with thionyl chloride (5.66ml, 0.078mol) and anhydrous methanol (23.5ml, 0.58mol). This gave the product as a white solid (5.805g, 97.4%).
^{1}H NMR (DMSO): δ 8.85 (3H,s,$NH_3^+Cl^-$), 3.72 (3H,s,OMe), 1.48 (6H,s,2xMe).
^{13}C NMR (DMSO): δ 172.8 (COOMe), 56.6 (OMe), 53.9 (CMe_2), 24.1 (2xMe).
MS ES$^+$: m/z 117.71 M+H$^+$, 142.88 M+Na$^+$.

Phenyl-(methyl-2-amino-2-methylpropanoate)-phosphorochloridate.

$C_{11}H_{15}O_4N_1Cl_1P_1$, MW=291.67.

[0078] This was synthesised according to **Standard Procedure 3,** using 2-amino-isobutyrate methyl ester hydrochloride (1.0g, 6.51mmol), $PhOP(O)Cl_2$ (1.37g, 0.97ml, 6.51mmol) and NEt_3 (1.32g, 1.18ml, 13.02mmol), to yield 1.73g (91%) of the crude product as an oil. This was stored in anhydrous THF (10ml) to give a solution of 0.593mmol/ml, and used without further purification.
^{31}P NMR: δ 6.86.
^{1}H NMR: δ 7.43-7.38 (2H,t,'*o*'-Ph), 7.32-7.21 (3H,m,'*m*'+'*p*'-Ph), 4.84 (1H,d,NHala), 3.83 (3H,s,OCH_3), 1.72 (6H,d, 2xCH_3).
^{13}C NMR: δ 175.7 (CO), 150.3 ('*ipso*'-Ph), 130.3 ('*m*'-Ph), 126.3 ('*p*'-Ph), 121.0 ('*o*'-Ph), 58.8 (OCH_3), 53.6 ($C[CH_3]_2$), 27.3 + 27.0 (2xCH_3).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl-(methoxy-α, αdimethylglycinyl)]-phosphate. Cf1584.

$C_{25}H_{32}O_5N_7P_1$, MW=542.23.

[0079] This was synthesised according to **Standard Procedure 4,** using (1S,4R)4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (300mg, 1.05mmol), tBuMgCl (1.0M solution in THF) (1.57ml, 1.57mmol) and phenyl-(methoxy-dimethylglycinyl)-phosphorochloridate (0.59M solution in THF) (5.3ml, 3.14mmol) in THF (20ml) stirring at room temperature for 96hrs. The crude product was purified by eluting with 3% MeOH in $CHCl_3$ and then with 2.5% MeOH in $CHCl_3$ to give the product as a white foam (193.7mg, 34.14%).
^{31}P NMR: δ 2.49.
^{1}H NMR: δ 7.40+7.36 (1H,d,H8), 7.24-7.19 (2H,t,'*o*'-Ph), 7.15-7.10 (2H,t,'*m*'-Ph), 7.07-7.02 (1H,t,'*p*'-Ph), 6.00-5.96 (2H, m,H2'+NHcPr), 5.80-5.76 (1H,m,H3'), 5.45-5.41 (1H,t,H1'), 4.99 (2H,bs,NH_2), 4.14-4.00 (3H,m,NHala+H5'), 3.62 (3H, s,OCH_3), 3.03 (1H,d, H4'), 2.91 (1H,d,CHcPr), 2.73-2.62 (1H,m,1of H6'), 1.62-1.51 (1H,m,1of H6'), 1.45-1.43 (6H,t, 2xCH_3), 0.78-0.71 (2H,q,2H of CH_2cPr), 0.54-0.49 (2H,t,2H of CH_2cycl.).
MS ES$^+$: m/z 541.9 (100%, M$^+$), 563.8 (30%, M+Na$^+$).
MS FAB: For $C_{25}H_{33}O_5N_7P$ requires 542.228081, found 542.228428.
HPLC: t_R 28.347 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).
IR: 3346.0 (N-Hstr.), 2923.0, 2853.5 (C-Hstr.), 1734.0 (C=Ostr.), 1590.2 (aromatic C-Cstr.), 1458.4 (C-Hdef.), 1376.8 (-CH_3sym.def.), 1261.3 (P=O), 1152.7 (C-Ostr.), 1028.0 (P-O-alkyl), 936.0 (olefinic C-Hdef.), 721.7 (monosub.aromatic C-Hdef.).

L-Aspartic acid dimethyl ester hydrochloride.

$C_6H_{12}O_4N_1Cl_1$, MW=197.62.

[0080] This was synthesised according to **Standard Procedure 1**, using L-asparagine (2.5g, 0.019mol) with thionyl chloride (3.67ml, 0.042mol) and anhydrous methanol (12.86ml, 0.32mol). This gave L-aspartic acid dimethyl ester hydrochloride in 3.70g, 99% yield.
^{1}H NMR (MeOH-d_4): δ 4.53-4.50 (1H,t,CH), 3.94 (3H,s,OCH_3), 3.85 (3H,s,OCH_3), 3.18 (2H,d,CH_2).
^{13}C NMR (MeOH-d_4): δ 170.4, 168.4 (CO), 53.0+52.0 (2xOMe), 49.4 (CH), 33.8 (CH_2).

Phenyl-(dimethoxy-L-aspartyl)-phosphorochloridate.

$C_{12}H_{15}O_6N_1Cl_1P_1$, MW=335.68.

[0081] This was synthesised according to **Standard Procedure 3,** using L-Aspartic acid dimethyl ester (1.0g, 5.04mmol), $PhOP(O)Cl_2$ (1.06g, 0.75ml, 5.04mmol) and NEt_3 (1.02g, 1.40ml, 10.1mmol) to yield 0.55g (32.4%) of crude product as an oil that was stored in anhydrous THF (5ml), to give a 0.33mmol/ml solution that was used without further purification.
^{31}P NMR: δ 9.74, 9.59 (1:1).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl-(L-asparic acid dimethyl ester)]-phosphate. Cf1 589.

$C_{24}H_{30}O_5N_7P_1$, MW=527.53.

[0082] This was synthesised according to **Standard Procedure 4,** using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (250mg, 0.87mol), tBuMgCl (1.0M solution in THF) (0.87ml, 0.87mmol) and phenyl-(L-aspartic acid dimethyl ester)-phosphorochloridate (0.50M solution in THF) (5.20ml, 2.62mmol) in THF (15ml) and stirring at room temperature for 48hrs. The crude product was purified by eluting with 2.5% MeOH in $CHCl_3$ (x2) to give the product as a pale yellow foam (163.5mg, 32.0%).
^{31}P NMR: δ 4.19, 3.76 (1:1).
^{1}H NMR: δ 7.40 (1H,d,H8), 7.24-7.19 (2H,t,'*o*'-Ph), 7.12-7.03 (3H,m,'*m*'+'*p*'-Ph), 6.05-5.95 (2H,m,H2'+NHcPr), 5.79 (1H,d,H3'), 5.44 (1H,s,H1'), 5.02 (2H,bs,NH_2), 4.38-4.07 (4H,m,H5',NHala+CHala), 3.61 (3H,s,OCH_3), 3.54 (3H,d, OCH_3), 3.05-2.52 (5H,m,CH_2aa,H4',CHcPr,+1 of H6'), 1.64-1.52 (1H,m,1 of H6'), 0.77-0.73 (2H,t,J=5.49Hz,2Hof CH_2cPr), 0.51 (2H,bs,2H of CH_2cPr).
^{13}C NMR: δ 173.3 (CO), 172.4 (CO), 161.5 (C2), 157.7 (C4), 152.3 (C8), 152.1 ('*ipso*'-Ph), 137.8 (C2'), 137.0 (C6), 132.6 (C3'), 131.1 ('*m*'-Ph), 126.4 ('*p*'-Ph), 121.6 ('*o*'-Ph), 116.2 (C5), 70.5 (C5'), 60.3 (C1'), 54.3 (OCH_3), 53.5 (OCH_3), 52.6 (CHala), 47.1 (C4'), 39.7 (CH_2ala), 36.0 (C6'), 25.1 (CHcPr), 8.8 (CH_2cPr).
MS ES$^+$: m/z 585.8 (100%, M$^+$), 607.7 (30%, M+Na$^+$).
MS FAB: For $C_{26}H_{33}O_5N_7P$ requires 586.217910, found 586.217510.
HPLC: t_R 29.261 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).
IR: 3347.5 (N-Hstr.), 2850.7 (C-Hstr.), 1739.9 (C=Ostr.), 1596.1 (aromatic C-Cstr.), 1461.9 (C-Hdef.), 1376.6 (-CH_3sym. def.), 1262.4 (P=O), 1211.2 (P-O-aryl), 1158.3 (C-Ostr.), 1027.0 (P-O-alkyl), 935.6 (olefinic C-Hdef.), 761.5, 722.0 (monosub.aromatic C-Hdef.).

3-cyclohexyl-L-alanine methyl ester hydrochloride salt

$C_9H_{19}N_1O_2Cl_1$, MW=221.75

[0083] This was synthesised according to **Standard Procedure 1**, using 3-cyclohexyl-L-alanine (3.0g, 17.5mmol), methanol (30ml), and thionyl chloride (2.56ml, 35mmol). The product was isolated as a white solid (3.23g, 83.9%).
^{1}H NMR (MeOH-d_4): δ 4.12-4.07 (3H,t,CHala), 3.85 (3H,s,OCH_3), 1.74-1.68 (6H,m,CH_2+*o*-CH_2), 1.56-1.43 (1H,m,CH), 1.36-1.15 (4H,m,*m*-CH_2), 1.05-0.90 (2H,q,*p*-CH_2).
^{13}C NMR: δ 170.15 (CO), 52.7 (OCH_3), 50.8 (CHala), 38.2 (CH_2), 33.6 (CH), 33.0+32.7 (2xCH_2-*o*), 26.3 (*p*-CH_2), 26.0+25.9 (2xCH_2-*m*).

Phenyl-(methoxy-3-cyclohexyl-L-alaninyl)-phosphorochloridate

$C_{16}H_{23}N_1O_4P_1Cl_1$, MW=359.82

[0084] This was synthesised according to **Standard Procedure 3,** using 3-Cyclohexyl-L-alanine methyl ester hydrochloride salt (0.7g, 316mmol), $PhOP(O)Cl_2$ (0.47ml, 3.16mmol), triethylamine (0.88ml. 6.31mmol) in DCM (60ml). The usual workup yielded the crude product as a yellow oil (1.18g, 100%), which was stored in THE (7ml) to give a 0.45M solution.

^{31}P NMR: δ 9.79, 9.49 (1:1).

^1H NMR:δ 7.49-7.43 (2H,m,'*o*'-Ph), 7.37-7.19 (3H,m,'*m*'+'*p*'-Ph). 4.46-4.35 (1H,q,NHala), 4.32-4.20 (1H,m,CHala), 3.88-3.85 (3H,dd,OCH_3), 1.94-1.90 (1H,d,CHcHx), 1.76-1.60

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-Phenyl-(methoxy-3-cyclohexane-L-alaninyl)-phosphate. Cf1709.

$C_{30}H_{40}N_7O_5P_1$, MW=609.66

[0085] This was synthesised according to **Standard Procedure 4**, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (150mg, 0.52mmol), tBuMgCl (1.05ml, 1.05mmol, of a 1.0M solution in THF), in THF (4ml) and phenyl-(methoxy-3-cyclohexane-L-alaninyl)-phosphorochloridate (3.5ml, 1.57mmol, of a 0.45M solution in THF), at room temperature for 24hrs. After 24hrs, additional phenyl-(methoxy-3-cyclohexane-L-alaninyl)-phosphorochloridate (2.5ml, 1.12mmol, of a 0.45M solution in THF) was added and the reaction stirred for another 24hrs. The crude product was purified by eluting with 3% MeOH in $CHCl_3$, and then 2.5% MeOH in $CHCl_3$ to give the pure product as a pale yellow foamy solid (79.6mg, 24.9%).

^{31}P NMR: δ 4.14, 3.98 (1:1).

^1H NMR: δ 7.50 (1H,d,H8), 7.34-7.13 (5H,t,OPh), 6.20 (1H,s,NHcPr), 6.08 (1H,t,H2'), 5.89 (1H,q,H3'), 5.53 (1H,bs, H1'), 5.16 (2H,bs,NH_2), 4.24-3.84 (4H,m,H5',NHala+CHala), 3.66 (3H,s,OCH_3), 3.34 (1H,bs,), 3.11 (1H,d,), 3.03 (1H, bs,), 2.84-2.72 (1H,m,1of H6'), 1.98-1.36 (8H,m,), 1.11 (3H,bs,), 0.89-0.83 (4H,m,2Hof cPr+CH_2-'*p*'), 0.63 (2H,d,2Hof cPr).

^{13}C NMR: δ 174.8CO 160.2 (C2), 156.5 (C4), 151.3 (C6), 151.2 ('*ipso*'-Ph), 136.8 (C2'), 135.9 (C8), 131.5 (C3'), 130.0 ('*m*'-Ph), 125.2 ('*p*'-Ph), 120.5 ('*o*'-Ph), 115.1 (C5), 69.4 (C5'), 59.3 (C1'), 52.7 (CHala), 46.1 (C4'), 42.5 (CH_2), 34.9 (C6'), 33.8 (CHcHx), 32.7 (CH_2-'*o*'), 26.7 (CH_2-'*m*'), 26.4 (CH_2-'*p*'), 24.2 (CHcPr), 7.8 (CH_2cPr).

MS ES+: m/z 610.3 (40%, M^+), 632.3 (100%, M+Na^+), 633.3 (25%, M+H+Na^+).

MS FAB: For $C_{30}H_{40}O_5N_7NaP$ requires 632.2726, found 632.2727.

HPLC: t_R 42.154 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-(L-alaninyl)-phosphate diammonium salt. Cf1540.

[0086] (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl-(methoxy-L-alaninyl)]-phosphate (125mg, 0.24mmol) was stirred in H_2O:NEt_3 (10ml, 1:1 v/v), at 25-35°C for 5hrs. The reaction mixture was extracted with DCM (8x20ml), and the aqueous layer reduced to dryness. The resulting solid was solubilised in isopropanol and purified by flash column chromatography, gradient eluting with i-PrOH:H_2O:NH_3 (11:1:1 to 9:1:2). The appropriate fractions were reduced to dryness and freeze dried to give the pure product as a white foamy solid (106mg, 95%).

^{31}P NMR (D_2O):- δ 8.62 (s).

^1H NMR (D_2O):- δ 7.79 (1H,s,H8), 6.08 (1H,d,H2'), 5.77 (1H,d,H3'), 5.35 (1H,t,H1'), 3.71-3.58 (2H,m,H5'), 3.41-3.32 (1H,m,CHa.a), 3.02-2.94 (1H,m,NHCH), 2.70-2.59 (2H,m,H4'+1 of CH_2), 1.57-1.49 (1H,dt,1 of CH_2), 1.10 (3H,d,CH_3), 0.83-0.76 (2H,q,1 of CH_2cyclo.), 0.61-0.56 (2H,q,1 of CH_2cyclo.).

MS ES+ : m/z 437.9 (100%, M^+).

MS FAB: calculated m/z 438.165481, found m/z 438.163790.

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-(D-alaninyl)-phosphate diammonium salt.

[0087] (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl-(methoxy-D-alaninyl)]-phosphate (100mg, 0.19mmol) was stirred in H_2O:NEt_3 (8ml, 1:1 v/v), for 16hrs. The reaction mixture was extracted with DCM (5x20ml), and the aqueous layer reduced to dryness. The resulting solid was solubilised in iso-

propanol and purified by flash column chromatography, gradient eluting with i-PrOH:H_2O:NH_3 (11:1:1 to 9:1:2). The appropriate fractions were reduced to dryness and freeze dried to give the pure product as a white foamy solid (88%).
^{31}P NMR (MeOH-d_4):- δ 7.81 (s).
^1H NMR:- δ 7.74 (1H,s,H8), 6.12 (1H,d,J=5.53Hz,H2'), 5.78 (1H,t,H3'), 5.44 (1H,d,J=6.21Hz,H1'), 3.74 (2H,t,J=5.42Hz, H5'), 3.70-3.60 (1H,m,CHala), 3.01 (1H,bs,H4'), 2.84 (1H,d,J=3.28Hz,CHcPr), 2.73-2.63 (1H,dt,J=8.66Hz+5.17Hz,1 of H6'), 1.67-1.58 (1H,m,1 of CH_2), 1.21 (3H,d,J=7.01Hz,CH_3ala), 0.79-0.73 (2H,q,J=6.68Hz,2H of CH_2cPr), 0.53 (2H, t,2H of CH_2cPr).
^{13}C NMR: δ 179.8 (CO), 161.2 (C2), 157.1 (C4), 151.1 (C6), 139.5 (C2'), 137.8 (C8), 130.7 (C3'), 114.6 (C5), 68.0 (C5'), 60.5 (C1'), 51.9 (CHala), 47.6 (C4'), 35.9 (C6'), 24.4 (CHcPr), 21.7 (CH_3ala), 7.6 (CH_2cPr).
MS ES$^+$: m/z 437.9 (100%, M^+).
MS FAB: calculated m/z 438.165481, found m/z 438.167842.

Phenyl-(ethoxy-L-alaninyl)-phosphorochloridate.

$C_{11}H_{15}O_4N_1Cl_1P_1$, MW=291.67.

[0088] This was synthesised according to **Standard Procedure 3,** using L-Alanine ethyl ester hydrochloride (1.0g, 6.51mmol), $PhOP(O)Cl_2$ (1.37g, 0.97ml, 6.51mmol) and NEt_3 (1.32g, 1.81ml, 13.0mmol) to yield 1.85g (97.4%) of crude product as an oil that was stored in anhydrous THF (10ml), to give a 0.63mmol/ml solution that was used without further purification.
^{31}P NMR: δ 9.41, 9.16 (1:1).
^1H NMR: δ 7.42-7.35 (2H,dd, '*o*'-Ph), 7.31-7.25 (3H,m,'*m*'+'*p*'-Ph); 4.71 (1H,d,NHala), 4.31-4.13 (3H,m,OCH_2+CHala), 1.55-1.52 (3H,dd,$OCH_2\underline{CH_3}$), 1.33-1.30 (3H,dd,CH_3ala).
^{13}C NMR: δ 173.1 (CO), 150.2 ('*ipso*'-Ph), 130.3 (*'m'*-Ph), 126.4 (*'p'*-Ph), 120.9 (*'o'*-Ph), 62.3 (OCH_2), 51.0 (CHala), 20.9 ($CH_2\underline{CH_3}$), 14.5 (CH_3ala).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl-(ethoxy-L-alaninyl)]-phosphate. Cf1587.

$C_{24}H_{30}O_5N_7P_1$, MW=527.53.

[0089] This was synthesised according to **Standard Procedure 4,** using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (300mg, 1.4mmol), tBuMgCl (1.0M solution in THF) (1.57ml, 1.57mmol), and phenyl-(ethoxy-L-alaninyl)-phosphorochloridate (0.49M solution in THF) (6.45ml, 3.14mmol) in anhydrous THF (20ml), and stirring at room temperature for 24hrs. The crude product was purified by column chromatography eluting with 2.5% MeOH in $CHCl_3$ to give the product as a pale yellow foam (290mg, 51.1%).
^{31}P NMR: δ 4.04, 3.96 (1:1).
^1H NMR: δ 7.39 (1H,d,J=7.56Hz,H8), 7.23-7.18 (2H,t,J=7.90Hz,'*o*'-Ph), 7.12-7.10 (2H,t,'*m*'-Ph), 7.06-7.01 (1H,t, J=7.13Hz,'*p*'-Ph), 6.18 (1H,bs,NHcPr), 5.97-5.95 (1H,t,H2'), 5.79-5.75 (1H,t,J=5.55Hz,H3'), 5.43 (1H,s,H1'), 5.13 (2H, bs,NH_2), 4.30-4.14 (1H,m,NHala), 4.06-4.00 (4H,m,H5'+OCH_2), 3.96-3.84 (1H,m,CHala), 3.03 (1H,d,J=5.74Hz,H4'), 2.92 (1H,bs,CHcPr), 2.71-2.61 (1H,m,1of H6'), 1.60-1.51 (1H,m,1 of H6'), 1.29-1.24 (3H,t,J=6.64Hz,CH_3ala), 1.18-1.11 (3H,m,$CH_2\underline{CH_3}$), 0.75-0.71 (2H,q,J=6.76Hz,2H of CH_2cPr), 0.50 (2H,bs,2H of CH_2cPr).
^{13}C NMR: δ 173.35 (CO), 159.8 (C2), 156.0 (C4), 150.6 (C6) 150.4('*ipso*'-Ph), 136.1 (C2'), 135.1 (C8), 130.8 (C3'), 129.3 ('*m*'-Ph), 124.5 ('*p*'-Ph), 119.8 ('*o*'-Ph), 114.4 (C5), 68.6 (C5'), 61.2 (OCH_2), 58.5 (C1'), 50.0 (CHala), 45.3 (C4'), 34.3 (C6'), 23.4 (CHcPr), 20.6 (CH_3ala), 13.8 ($CH_2\underline{CH_3}$), 7.0 (CH_2cPr).
MS ES$^+$: m/z 541.9 (100%, M^+), 546.84 (28%, M+H^+), 563.8 (25%, M+Na^+).
MS FAB: For $C_{25}H_{33}O_5N_7P$, requires 542.228081, found 542.228131.
HPLC: t_R 31.76, 32.03 (100%)-(100% water (0mins) 20% water (35mins), 20% water (45mins), 100% water (55mins)).
IR: 3334.1 (N-Hstr.), 1734.5 (C=Ostr.), 1595.9, 1488.0 (aromatic C-Cstr.), 1450.3 (C-Hdef.), 1394.2 (-CH_3sym.def.), 1252.8 (P=O), 1210.4 (P-O-aryl), 1153.3 (C-Ostr.), 1026.0 (P-O-alkyl), 934.8 (olefinic C-Hdef.), 759.0 (monosub.aromatic C-Hdef.).

Phenyl-(benzoxy-L-alaninyl)-phosphorochloridate.

$C_{16}H_{17}O_4N_1Cl_1P_1$, MW=353.74.

[0090] This was synthesised according to **Standard Procedure 3**,using L-alanine benzyl ester hydrochloride (1.0g,

4.64mmol), $PhOP(O)Cl_2$ (0.98g, 0.69ml, 4.64mmol) and NEt_3 (0.94g, 1.29ml, 9.27mmol) to yield 1.61g (98.2%) of crude product that was stored in anhydrous THF (10ml), to give a 0.46mmol/ml solution that was used without further purification.

^{31}P NMR: δ 9.41, 9.23 (1:1).

^1H NMR: δ 7.41-7.21 (10H,m,2xPh), 5.24 (2H,d,$\underline{CH_2}$Ph), 4.95-4.88 (1H,t,NHala), 4.36-4.15 (1H,m,CHala), 1.56 (3H, t,CH_3ala).

^{13}C NMR: δ 172.9 (CO), 150.2 ('*ipso*'-OPh), 135.5 ('*ipso*'-CH_2Ph), 130.3 ('*m*'-OPh), 129.0 ('*o*'-CH_2Ph), 128.7 ('*m*'+'*p*'-CH_2Ph), 126.4 ('*p*'-OPh), 121.0 ('*o*'-OPh), 68.0 (OCH_2), 51.1 (CHala), 20.8 (CH_3ala).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl-(benzoxy-L-alaninyl)]-phosphate. Cf1582.

$C_{30}H_{35}O_5N_7P_1$, MW=603.6.

[0091] This was synthesised according to **Standard Procedure 4,** using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (400mg, 1.4mmol), tBuMgCl (1.0M solution in THF) (2.1ml, 2.1mmol), and phenyl-(benzoxy-L-alaninyl)-phosphorochloridate (0.46M solution in THF) (9.2ml, 4.19mmol) in anhydrous THF (20ml), and stirring at room temperature for 64hrs. The crude product was purified by column chromatography eluting with 3% MeOH in $CHCl_3$, and then 2.5% MeOH in $CHCl_3$ to give the product as a white foam (82.2mg, 9.75%).

A second synthesis was undertaken with (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (200mg, 0.7mmol), tBuMgCl (2.43ml of a 1.0M soln in THF, 2.43mmol), and phenyl-(benzoxy-L-alaninyl)-phosphorochloridate (2.2ml of a 0.46M soln in THF, 2.1mmol) in THF (2.5ml). Purification by column chromatography eluting with 3% MeOH in $CHCl_3$ gave the pure product as a white foamy solid (90mg, 21.3%).

^{31}P NMR: δ 3.82, 3.72 (1:1).

^1H NMR: δ 7.51 (1H,d,H8), 7.37-7.15 (10H,m,OPh+$CH_2\underline{Ph}$), 6.10-6.04 (1H,m,H2'), 5.96 (1H,bs,NHcPr), 5.89 (1H,dd, J=5.36Hz,H3'), 5.54 (1H,t,H1'), 5.16 (2H,bs,NH_2), 4.96 (2H,bs,$\underline{CH_2}$Ph), 4.23-4.05 (3H,m,NHala+H5'), 3.89-3.70 (1H, dt,CHala), 3.16-3.12 (1H,t,H4'), 3.03 (1H,bs,CHcPr), 2.85-2.71 (1H,m,1of H6'), 1.74-1.64 (1H,m,1of H6'), 1.44-1.39 (3H,t,J=7.84Hz,CH_3ala), 0.88 (2H,q,J=6.75Hz,2H of CH_2cPr), 0.64 (2H,m,2H of CH_2cPr).

^{13}C NMR: δ 173.3 (CO), 159.7 (C2), 156.0 (C4), 150.9 (C6), 150.7 ('*ipso*'-OPh), 136.4 (C2'), 135.7 ('*ipso*'-Bn), 135.2 (C8), 131.0 (C3'), 129.6 ('*o*'-Bn), 128.6 ('*m*'-Bn), 128.5 ('*p*'-Bn), 128.2 ('*m*'-OPh), 124.9 ('*p*'-OPh), 120.1 ('*o*'-OPh), 114.8 (C5), 68.8 (C5'), 67.2 ($\underline{CH_2}$Ph), 58.9 (C1'), 50.3 (CHala), 45.6 (C4'), 34.4 (C6'), 23.7 (CHcPr), 21.0 (CH_3ala), 7.4 (CH_2cPr).

MS ES$^+$: m/z 603.8 (100%, M$^+$), 604.8 (30%, M+H$^+$), 625.7 (20%, M+Na$^+$).

MS FAB: For $C_{30}H_{35}O_5N_7P$ requires 604.243731, found 604.241775.

HPLC: t_R 33.39 (99.7%)-(100% water (0mins) 20% water (35mins), 20% water (45mins), 100% water (55mins)).

IR: 3355.9 (N-Hstr.), 2923.3, 2853.7 (C-Hstr.), 1734.1 (C=Ostr.), 1595.6 (aromatic C-Cstr.), 1458.4 (C-Hdef.), 1376.5 (-CH_3sym.def.), 1154.4 (C-Ostr.), 1028.2 (P-O-alkyl), 935.8 (olefinic C-Hdef.), 721.7 (monosub.aromatic C-Hdef.).

L-Alanine *n*-propyl ester hydrochloride salt.

$C_6H_{14}N_1O_2Cl_1$, MW=167.634

[0092] This was synthesised according to **Standard Procedure 1,** using anhydrous propan-1-ol (42.0ml, 0.56mol), thionyl chloride (8.2ml, 0.112mol) and L-alanine (5.0g, 0.056mol). The product was isolated as a white solid (8.88g, 94.3%).

^1H NMR (MeOH-d_4): δ 4.34-4.26 (2H,m,OCH_2), 4.24-4.17 (1H,q,CHala), 1.88-1.78 (2H,m,CH_2), 1.65 (3H,d,J=7.24Hz, CH_3ala), 1.10-1.05 (3H,t,$CH_2\underline{CH_3}$).

^{13}C NMR: δ 170.1 (CO), 68.0 (OCH_2), 48.9 (CHala), 21.9 (CH_2), 15.3 (CH_3ala), 9.5 ($CH_2\underline{CH_3}$).

Phenyl-(*n*-propoxy-L-alaninyl)-phosphorochloridate

$C_{12}H_{17}N_1O_4P_1Cl_1$, MW=305.79

[0093] This was synthesised according to **Standard Procedure 3,** using L-Alanine *n*-propyl ester hydrochloride salt (0.5g, 2.98mmol), $PhOP(O)Cl_2$ (0.45ml, 2.98mmol), triethylamine (0.83ml. 5.97mmol) in DCM (70ml). The usual workup yielded the crude product as a yellow oil (0.84g, 92.1%), which was stored in THF (5ml) to give a 0.55M solution.

^{31}P NMR: δ 9.41, 9.17 (1:1).

^{13}C NMR: δ 173.1 (CO), 150.1 ('*ipso*'-Ph), 130.0 ('*m*'-Ph), 126.4 ('*p*'-Ph), 121.0 ('*o*'-Ph), 67.9 (OCH_2), 51.0 (CHala),

22.3 ($\underline{CH_2}CH_3$), 21.0 (CH_3ala), 10.7 ($CH_2\underline{CH_3}$).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-Phenyl-(*n*-propoxy-L-alaninyl)-phosphate. Cf1646.

$C_{26}H_{34}N_7O_5P_1$, MW=555.57

[0094] This was synthesised according to **Standard Procedure 4**, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (100mg, 0.35mmol), tBuMgCl (0.7ml, 0.7mmol, of a 1.0M solution in THF), in THE (3ml) and phenyl-(*n*-propyl-L-alaninyl)-phosphorochloridate (1.9ml, 1.05mmol, of a 0.55M solution in THF), at room temperature for 24hrs. The crude product was purified by eluting with 3% MeOH in $CHCl_3$ to give the pure product as a pale yellow foamy solid (123mg, 63.4%).
^{33}P NMR: δ 4.06, 3.98 (1:1).
^1H NMR: δ 7.40 (1H,d,J=7.99Hz,H8), 7.23-7.18 (2H,dd,'*o*'-Ph), 7.12-7.02 (3H,m,'*m*'+'*p*'-Ph), 6.16 (1H,bs,H3'), 5.96 (1H,t,H2'), 5.78 (1H,d,J=5.83Hz,NHcycl), 5.44 (1H,bs,H1'), 5.15 (2H,bs,NH_2), 4.33-4.18 (1H,m,CHala), 4.15-4.04 (2H, m,OCH_2), 4.01-3.88 (2H,m,H5'), 3.65 (1H,bs,NHala), 3.03 (1H,d,H4'), 2.92 (1H,bs,CHcycl), 2.72-2.62 (1H,m,1 of H6'), 1.60-1.47 (3H,m,lof H6'+$\underline{CH_2}CH_3$), 1.30-1.26 (3H,t,CH_3ala), 0.84-0.80 (3H,m,$CH_2\underline{CH_3}$), 0.73 (2H,d,J=6.8Hz,1 of CH_2cycl), 0.51 (2H,bs, 1 of CH_2cycl).
^{13}C NMR: δ 174.1CO 160.4 (C2), 156.6 (C4), 151.1 (C6+'*ipso*'-Ph), 136.8 (C2'), 135.9 (C8), 131.5 (C3'), 130.0 ('*m*'-Ph), 125.2 ('*p*'-Ph), 120.5 ('*o*'-Ph), 115.0 (C5), 69.2 (C5'), 67.4 (OCH_2), 59.2 (C1'), 50.6 (CHala), 46.0 (C4'), 35.0 (C6'), 24.2 (CHcPr), 22.3 ($\underline{CH_2}CH_3$), 21.5 (CH_3ala), 10.7 ($CH_2\underline{CH_3}$), 7.7 (CH_2cycl).
MS ES+: m/z 555.8 (100%, M^+), 557.0 (30%, $M+H^+$).
MS FAB: For $C_{26}H_{35}O_5N_7P$ requires 556.2437, found 556.2438.
HPLC: t_R 34.708 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).

L-Alanine n-butyl ester hydrochloride salt.

$C_7H_{16}N_1O_2Cl_1$, MW=181.661

[0095] This was synthesised according to **Standard Procedure 1**, using anhydrous butan-1-ol (51.4ml, 0.56mol), thionyl chloride (8.2ml, 0.112mol) and L-alanine (5.0g, 0.056mol). The product was isolated as a white solid (8.86g, 86.9%).
^1H NMR (MeOH-d_4): δ 4.29-4.17 (2H,m,OCH_2), 4.13-4.06 (1H,q,CHala), 1.71-1.62 (2H,m,$OCH_2\underline{CH_2}$), 1.53 (3H,d, J=7.25Hz,CH_3ala), 1.47-1.34 (2H,m,$\underline{CH_2}CH_3$), 0.96-0.91 (3H,t,$CH_2\underline{CH_3}$).
^{13}C NMR: δ 170.1 (CO), 66.2 (OCH_2), 48.9 (CHala), 30.6 ($OCH_2\underline{CH_2}$), 19.0 ($\underline{CH_2}CH_3$). 15.3 (CH_3ala), 13.0 ($CH_2\underline{CH_3}$).

Phenyl-(*n*-butoxy-L-alaninyl)-phosphorochloridate

$C_{13}H_{19}N_1O_4P_1Cl_1$, MW=317.82

[0096] This was synthesised according to **Standard Procedure 3**, using L-Alanine *n*-butyl ester hydrochloride salt (0.5g, 2.75mmol), $PhOP(O)Cl_2$ (0.41ml, 2.75mmol), triethylamine (0.77ml. 5.5mmol) in DCM (80ml). The usual workup yielded the crude product as a yellow oil (0.84g, 94.5%), which was stored in THF (5ml) to give a 0.525M solution.
^{31}P NMR: δ 9.39, 9.10 (1:1).
^1H NMR: δ 7.43-7.15 (5H,m,Ph), 4.68-4.59 (1H,q,CHala), 4.27-4.05 (3H,m,OCH_2+NHala), 1.73-1.59 (2H,m, $OCH_2\underline{CH_2}$), 1.56-1.53 (2H,dd,$\underline{CH_2}CH_3$), 1.46-1.37 (3H,m,CH_3ala), 1.00-0.92 (3H,m,$CH_2\underline{CH_3}$).
^{13}C NMR: δ 173.2 (CO), 150.1 ('*ipso*'-Ph), 130.3 ('*m*'-Ph), 126.4 ('*p*'-Ph), 121.0 ('*o*'-Ph), 66.2 (OCH_2), 51.0 (CHala), 30.9 ($OCH_2\underline{CH_2}$), 21.0 (CH_3ala), 19.4 ($\underline{CH_2}CH_3$), 14.1 ($CH_2\underline{CH_3}$).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-Phenyl-(*n*-butoxy-L-alaninyl)-phosphate. Cf1647.

$C_{27}H_{36}N_7O_5P_1$, MW=569.597

[0097] This was synthesised according to **Standard Procedure 4**, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (100mg, 0.35mmol), tBuMgCl (0.7ml, 0.7mmol, of a 1.0M solution in THF), in THF (3ml) and phenyl-(*n*-butyl-L-alaninyl)-phosphorochloridate (2.0ml, 1.05mmol, of a 0.525M solution in THF), at room temperature for 24hrs. The crude product was purified by eluting with 3% MeOH in $CHCl_3$ to give the pure product

as a pale yellow foamy solid (157mg, 78.9%).
^{31}P NMR: δ 4.01, 3.95(1:1).
^{1}H NMR: δ 7.40 (1H,d,J=7.32Hz,H8), 7.23-7.18 (2H,t,'o'-Ph), 7.11 (2H,t,'*m*'-Ph), 7.04 (1H,t,'*p*'-Ph), 6.02 (1H,bs,H3'), 5.97 (1H,t,H2'), 5.78 (1H,bs,NHcycl), 5.44 (1H,bs,H1'), 5.06 (2H,bs,NH_2), 4.22-3.88 (6H,m,CHala,OCH_2,H5'+NHala), 3.05 (1H,d,H4'), 2.93 (1H,bs,CHcycl), 2.72-2.62 (1H,m,1 of H6'), 1.61-1.47 (3H,m,lof H6'+$OCH_2\underline{CH_2}$), 1.30-1.26 (5H, t,CH_3ala+$\underline{CH_2}CH_3$), 0.85-0.80 (3H,t,$CH_2\underline{CH_3}$), 0.74 (2H,d,J=6.45Hz, 1 of CH_2cycl), 0.51 (2H,bs, 1 of CH_2cycl).
^{13}C NMR: δ 174.1(CO), 160.4 (C2), 156.7 (C4), 151.2 (C6), 151.1 ('*ipso*'-Ph), 136.7 (C2'), 135.8 (C8), 131.5 (C3'), 130.0 ('*m*'-Ph), 125.2 ('*p*'-Ph), 120.5 ('*o*'-Ph), 115.0 (C5), 69.3
(C5'), 65.8 (OCH_2), 59.2 (C1'), 50.6 (CHala), 46.0 (C4'), 35.0 (C6'), 30.9 ($OCH_2\underline{CH_2}$), 24.1 (CHcPr), 21.5 (CH_3ala), 19.4 ($\underline{CH_2}CH_3$), 14.1 ($CH_2\underline{CH_3}$), 7.8 (CH_2cycl).
MS ES$^+$: m/z 569.9 (70%, M^+), 570.9 (20%, M+H$^+$), 591.8 (100%, M+Na$^+$), 607.8 (20%, M+K$^+$).
HPLC: t_R 38.27 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).

L-Alanine *i*-propyl ester hydrochloride salt.

$C_6H_{14}N_1O_2Cl_1$, MW=167.634

[0098] This was synthesised according to **Standard Procedure 1**, using anhydrous propan-2-ol (43.0ml, 0.56mol), thionyl chloride (8.2ml, 0.112mol) and L-alanine (5.0g, 0.056mol). The product was isolated as a semicrystalline solid (8.86g, 86.9).
^{1}H NMR (MeOH-d_4): δ 5.16-5.08 (1H,m,CHala), 4.11-4.04 (1H,q,$O\underline{CH}(Me)_2$), 1.55 (3H,d,J=7.21Hz,CH_3ala), 1.34-1.31 (6H,dd,$CH(\underline{Me})_2$).
^{13}C NMR: δ 169.5 (CO), 70.8 ($CO\underline{CH}(Me)_2$), 48.9 (CHala), 20.8 (CH_3ala), 15.3 ($CH(\underline{Me})_2$).

Phenyl-(*i*-propoxy-L-alaninyl)-phosphorochloridate

$C_{12}H_{17}N_1O_4P_1Cl_1$, MW=305.79

[0099] This was synthesised according to **Standard Procedure 3,** using L-Alanine *i*-propyl ester hydrochloride salt (0.5g, 2.98mmol), $PhOP(O)Cl_2$ (0.45ml, 2.98mmol), triethylamine (0.83ml. 5.97mmol) in DCM (70ml). The usual workup yielded the crude product as a yellow oil (1.12g, >100%), which was stored in THF (5ml) to give a 0.597M solution.
^{31}P NMR: δ 9.45, 9.17 (1:1).
^{13}C NMR: δ 172.6 (CO), 150.2 ('*ipso*'-Ph), 130.3 ('*m*'-Ph), 126.4 ('*p*'-Ph), 121.0 ('*o*'-Ph), 70.1 (OCH), 51.1 (CHala), 22.1 ($CH(\underline{CH_3})_2$), 20.9 (CH_3ala).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-Phenyl-(*i*-propoxy-L-alaninyl)-phosphate. Cf1661.

$C_{26}H_{34}N_7O_5P_1$, MW=555.57

[0100] This was synthesised according to **Standard Procedure 4**, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (100mg, 0.35mmol), tBuMgCl (0.7ml, 0.7mmol, of a 1.0M solution in THF), in THE (3ml) and phenyl-(*i*-propyl-L-alaninyl)-phosphorochloridate (1.76ml, 1.05mmol, of a 0.597M solution in THF), at room temperature for 72hrs. The crude product was purified by eluting with 3% MeOH in $CHCl_3$ (x2) to give the pure product as a pale yellow foamy solid (106.8mg, 54.8%).
^{31}P NMR: δ 4.02, 3.98 (1:1).
^{1}H NMR: δ 7.41 (1H,d,J=8.12Hz,H8), 7.24-7.19 (2H,m,'o'-Ph), 7.13-7.03 (3H,m,'*m*'+'*p*'-Ph), 6.37 (1H,bs,,NHcPr), 5.98 (1H,t,H3'), 5.80-5.76 (1H,m,H2'), 5.43 (1H,bs,H1'), 5.21 (2H,bs,NH_2), 4.94-4.86 (1H,m,OCH), 4.15-3.98 (2H,m,H5'), 3.92-3.83 (1H,m,CHala), 3.59 (1H,bs,NHala), 3.06-2.98 (1H,m,H4'), 2.93 (1H,bs,CHcPr), 2.74-2.63 (1H,m,1 of H6'), 1.62-1.53 (1H,m,1 of H6'), 1.34-1.18 (3H,m,CH_3ala), 1.15-1.11 (6H,m,$CH(\underline{CH_3})_2$), 0.79-0.73 (2H,q,2H of CH_2cPr), 0.53 (2H,bs,2Hof CH_2cPr).
^{13}C NMR: δ 173.5(CO) 159.8 (C2), 156.2 (C4), 151.1 (C6), 151.0 ('*ipso*'-Ph), 136.9 (C2'), 136.1 (C8), 131.3 (C3'), 130.0 ('*m*'-Ph), 125.3 ('*p*'-Ph), 120.5 ('*o*'-Ph), 115.0 (C5), 69.6 (C5'), 69.2 (OCH), 59.3 (C1'), 50.7 (CHala), 46.0 (C4'), 34.9 (C6'), 24.2 (CHcPr), 22.0 ($CH(\underline{CH_3})_2$), 21.4 (CH_3ala), 7.8 (CH_2cycl).
□S ES$^+$: m/z 555.9 (100%, M^+), 556.9 (30%, M+H$^+$).
MS MALD/I TOF: For $C_{26}H_{35}O_5N_7P$ found 555.575.
HPLC: t_R 35.85 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).

Phenyl-*tert*butyloxy-L-alaninyl phosphorochloridate.

$C_{16}H_{17}O_4N_1Cl_1P_1$, MW=353.74.

[0101] This was synthesised according to **Standard Procedure 3,** using L-alanine *tert*-butyl ester hydrochloride (0.5g, 2.75mmol), $PhOP(O)Cl_2$ (0.41ml, 2.75mmol) and NEt_3 (0.77ml, 5.5mmol) to yield 0.77g (87.5%) of crude product that was stored in anhydrous THF (5ml), to give a 0.48mmol/ml solution that was used without further purification.
^{31}P NMR: δ 9.53, 9.20(1:1).
^1H NMR: δ 7.44-7.39 (2H,t,'*o*'-Ph), 7.32-7.26 (3H,m,'*m*'+'*p*'-Ph), 4.47-4.34 (1H,m,NHala), 4.17-4.04(1H,m,CHala), 1.53 (9H,3s,3xCH_3).
^{13}C NMR: δ 170.7 (CO), 148.7 ('*ipso*'-Ph), 128.9 ('*o*'-Ph), 124.9 ('*p*'-Ph), 119.5 ('*m*'-Ph), 81.65 ($\underline{C}Me_3$), 50.0 (CHala), 26.9 (3xCH_3).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl-*tert*butyloxy-L-alaninyl)-phosphate. Cf1645.

$C_{24}H_{30}O_5N_7P_1$, MW=603.6.

[0102] This was synthesised according to **Standard Procedure 4**, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (140mg, 0.52mmol), tBuMgCl (1.05ml, 1.05mmol of a 1.0M solution in THF), and phenyl-(*tert*butyloxy-L-alaninyl)-phosphorochloridate (3.3ml, 1.57mmol, of a 0.48M solution in THF), in anhydrous THE (4ml) stirring at room temperature for 48hrs. The crude product was purified by eluting with 3% MeOH in $CHCl_3$ to give the pure product as white foamy solid (192.3mg, 69.0%).
^{31}P NMR: δ 4.15 (s).
^1H NMR: δ 7.40 (1H,d,J=8.35Hz,H8), 7.23-7.18 (2H,t,'*m*'-Ph), 7.12 (2H,d,'*o*'-Ph), 7.06-7.02 (1H,t,'*p*'-Ph), 6.09 (1H,bs, H2'), 5.97 (1H,bs,H3'), 5.77 (1H,d,NHcPr), 5.44 (1H,bs,H1'), 5.10 (2H,bs,NH_2), 4.14-4.05 (3H,m,H5'+NHala), 3.85-3.77 (1H,q,CHala), 3.04 (1H,bs,H4'), 2.93 (1H,bs,CHcPr), 2.72-2.62 (1H,m,1 of H6'), 1.58-1.53 (1H,t,1 of H6'), 1.34 (9H,d, $C\underline{Me_3}$), 1.27-1.23 (3H,t,CH_3ala), 0.73 (2H,d,2Hof CH_2cPr), 0.51 (2H,bs,2HofCH_2cPr).
^{13}C NMR: δ 173.2 (CO), 160.4 (C2), 156.7 (C4), 151.2 (C6+'*ipso*'-Ph), 136.8 (C2'), 135.9 (C8), 131.5 (C3'), 130.0 ('*m*'-Ph), 125.2 ('*p*'-Ph), 120.6 ('*o*'-Ph), 115.2 (C5), 82.3 ($\underline{C}[CH_3]_3$), 69.3 (C5'), 59.1 (C1'), 46.0 (C4'), 35.0 (C6'), 28.3 (3xCH_3), 24.2 (CHcPr), 21.5 (CH_3ala), 7.8 (CH_2cPr).
MS ES$^+$: m/z 570.0 (100%, M^+), 570.9 (32%, $M+H^+$).
MS FAB: For $C_{27}H_{37}O_5N_7P$ requires 570.2594, found 570.2598.
HPLC: t_R 36.158 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).

L-Alanine *n*-pentyl ester hydrochloride salt

$C_8H_{18}N_1O_2Cl_1$, MW=195.69

[0103] This was synthesised according to **Standard Procedure 1,** using pentan-1-ol (36.3ml, 0.337mol), thionyl chloride (4.92ml, 67.4mmol) and L-Alanine (3.0g, 33.7mmol). The product was isolated as a white solid pure product (4.86g, 73.7%).
^1H NMR (MeOH-d_4): δ 4.32-4.20 (2H,m,OCH_2), 4.16-4.08 (1H,m,CHala), 1.77-1.68 (2H,m,$OCH_2\underline{CH_2}$), 1.56 (3H,d, J=7.22Hz,CH_3ala), 1.42-1.36 (4H,m,$\underline{CH_2}CH_2CH_3$), 0.97-0.93 (3H,m,$CH_2\underline{CH_3}$).
^{13}C NMR: δ 170.1 (CO), 66.5 (OCH_2), 48.8 (CHala), 28.2 ($OCH_2\underline{CH_2}$), 28.0 ($\underline{CH_2}CH_2CH_3$), 22.3 ($\underline{CH_2}CH_3$), 15.2 (CH_3ala), 13.3 ($CH_2\underline{CH_3}$).

Phenyl-(*n*-pentoxy-L-alaninyl)-phosphorochloridate

$C_{14}H_{21}N_1O_4P_1Cl_1$, MW=333.78

[0104] This was synthesised according to **Standard Procedure 3,** using L-Alanine *n*-pentyl ester hydrochloride salt (0.5g, 2.56mmol), $PhOP(O)Cl_2$ (0.38ml, 2.56mmol), triethylamine (0.71ml. 5.11mmol) in DCM (60ml). The usual workup yielded the crude product as a yellow oil (0.79g, 92.6%), which was stored in THF (5ml) to give a 0.47M solution.
^{31}P NMR: δ 9.39, 9.12 (1:1).
^1H NMR: δ 7.43-7.38 (2H,m,'*o*'-Ph), 7.32-7.25 (3H,m,'*m*'+'*p*'-Ph), 4.63 (1H,bd,NHala), 4.24-4.11 (3H,m,OCH_2+CHala), 1.73-1.65 (2H,m,$OCH_2\underline{CH_2}$), 1.57-1.53 (3H,dd,CH_3ala), 1.42-1.35 (4H,m,2xCH_2), 0.97-0.91 (3H,m,$CH_2\underline{CH_3}$).
^{13}C NMR: δ 173.1 (CO), 150.1 ('*ipso*'-Ph), 130.3 ('*m*'-Ph), 126.4 ('*p*'-Ph), 121.0 ('*o*'-Ph), 66.5 (OCH_2), 51.0 (CHala),

28.6 (CH_2-C2), 28.3 (CH_2-C3), 22.7 (CH_2-C4), 21.0 (CH_3ala), 14.1 (CH_3-C5).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-Phenyl-(*n*-pentyloxy-L-alaninyl)-phosphate. Cf1706.

$C_{28}H_{38}N_7O_5P_1$, MW=583.7

[0105] This was synthesised according to **Standard Procedure 4,** using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (100mg, 0.35mmol), tBuMgCl (0.7ml, 0.7mmol, of a 1.0M solution in THF), in THF (3ml) and phenyl-(*n*-pentyl-L-alaninyl)-phosphorochloridate (2.22ml, 1.05mmol, of a 0.47M solution in THF), at room temperature for 24hrs. The crude product was purified by eluting with 2.5-3.0% MeOH in $CHCl_3$ (x2) to give the pure product as a pale yellow foamy solid (143.2mg, 70.2%).
^{31}P NMR: δ 3.99, 3.95 (1:1).
^1H NMR: δ 7.41 (1H,d,J=7.18Hz,H8), 7.24-7.19 (2H,m,'o'-Ph), 7.12-7.02 (3H,m,'*m*'+'*p*'-Ph), 6.09 (1H,bs,NHcPr), 5.98 (1H,d,H2'), 5.79 (1H,bs,H3'), 5.44 (1H,bs,H1'), 5.09 (2H,bs,NH_2), 4.16-3.88 (6H,m,CHala,OCH_2,H5'+NHala), 3.05 (1H, bs,H4'), 2.94 (1H,bs,CHcPr), 2.73-2.63 (1H,m,1of H6'), 1.62-1.51 (3H,m,1of H6'+$OCH_2\underline{CH_2}$), 1.31-1.21 (7H,t, CH_3ala+2xCH_2), 0.81-0.74 (5H,m,CH_3+2Hof CH_2cPr), 0.52 (2H,bs,2Hof CH_2cPr).
^{13}C NMR: δ 174.1(CO), 160.1 (C2), 156.5 (C4), 151.2 (C6), 151.1 ('*ipso*'-Ph), 136.8 (C2'), 136.1 (C8), 131.5 (C3'), 130.0 ('*m*'-Ph), 125.2 ('*p*'-Ph), 120.5 ('*o*'-Ph), 115.1 (C5), 69.3 (C5'), 66.1 (OCH_2), 59.3 (C1'), 50.7 (CHala), 46.0 (C4'), 34.9 (C6'), 28.6 (CH_2-C2), 28.3 (CH_2-C3), 24.2 (CHcPr), 22.6 (CH_2-C4), 21.5 (CH_3ala), 14.3 (CH_3-C5), 7.8 (CH_2cPr).
MS ES+: m/z 584.2 (100%, M^+), 585.2 (25%, $M+H^+$).
MS FAB: For $C_{28}H_{39}O_5N_7P$ requires 584.2750, found 584.2757.
HPLC: t_R 40.294 (99.3%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).

L-Alanine *n*-hexyl ester hydrochloride salt

$C_9H_{20}N_1O_2Cl_1$, MW=209.75

[0106] This was synthesised according to **Standard Procedure 2,** using L-Alanine (2.0g, 22.5mmol), hexan-1-ol (2.82ml, 22.5mmol), *p*-toluene sulfonic acid monohydrate (4.7g, 24.7mmol), and toluene (100ml). L-alanine *n*-hexyl ester hydrochloride was isolated as a white powdery solid (3.32g, 70.5%).
^1H NMR (MeOH-d_4): δ 4.31-4.18 (2H,m,OCH_2), 4.17-4.09 (1H,q,CHala), 1.75-1.66 (2H,m,$OCH_2\underline{CH_2}$), 1.57 (3H,d, J=7.20Hz,CH_3ala), 1.45-1.35 (6H,m,$[\underline{CH_2}]_3CH_3$), 0.94-0.89 (3H,t,$CH_2\underline{CH_3}$).
^{13}C NMR: δ 170.1 (CO), 66.5 (OCH_2), 48.9 (CHala), 31.6 ($OCH_2\underline{CH_2}$), 28.6 ($O[CH_2]_2\underline{CH_2}$), 25.6 ($\underline{CH_2}CH_2CH_3$), 22.6 ($\underline{CH_2}CH_3$), 15.4 ($CH_3$ala), 13.4 ($CH_2\underline{CH_3}$).

Phenyl-(*n*-hexyloxy-L-alaninyl)-phosphorochloridate

$C_{15}H_{23}N_1O_4P_1Cl_1$, MW=347.81

[0107] This was synthesised according to **Standard Procedure 3,** using L-Alanine n-hexyl ester hydrochloride salt (0.5g, 2.38mmol), $PhOP(O)Cl_2$ (0.36ml, 2.38mmol), triethylamine (0.66ml. 4.77mmol) in DCM (60ml). The usual workup yielded the crude product as a yellow oil (0.69g, 83.2%), which was stored in THE (4ml) to give a 0.496M solution.
^{31}P NMR: δ 9.40, 9.10 (1:1).
^1H NMR: δ 7.44-7.14 (5H,m,OPh), 4.25 (1H,bs,NHala), 4.23-4.03 (3H,m,OCH_2+CHala), 1.70-1.63 (2H,m,CH_2-2), 1.57-1.54 (2H,m,CH_2-3), 1.47-1.32 (7H,m,CH_3ala+2CH_2-4,5), 0.93-0.91 (3H,dd,CH_3-6).
^{13}C NMR: δ 173.2 (CO), 150.1 ('*ipso*'-Ph), 130.3 ('*m*'-Ph), 126.4 ('*p*'-Ph), 120.9 ('*o*'-Ph), 66.4 (OCH_2), 51.0 (CHala), 31.7 (CH_2-C2), 28.9 (CH_2-C3), 25.8 (CH_2-C4), 22.9 (CH_2-C5), 21.0 (CH_3ala), 14.4 (CH_3-C6).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-Phenyl-(*n*-hexyloxy-L-alaninyl)-phosphate.

$C_{29}H_{40}N_7O_5P_1$, MW=597.651

[0108] This was synthesised according to **Standard Procedure 4,** using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (100mg, 0.35mmol), tBuMgCl (0.7ml, 0.7mmol, of a 1.0M solution in THF), in THF (3ml) and phenyl-(*n*-hexoxy-L-alaninyl)-phosphorochloridate (2.11ml, 1.05mmol, of a 0.496M solution in THE), at room temperature for 24hrs. Additional phenyl-(*n*-hexoxy-L-alaninyl)-phosphorochloridate (1.5ml, 0.68mmol, of a

0.496M solution in THF), was added and the reaction stirred for a further 24hrs. The crude product was purified by eluting with 3.0% MeOH in $CHCl_3$ (x2) to give the pure product as a pale yellow foamy solid.
^{31}P NMR: δ 3.94, 3.91 (1:1).
^{1}H NMR: δ 7.52 (1H,d,J=8.00Hz,H8), 7.36-7.31 (2H,m,'o'-Ph), 7.25-7.15 (3H,m,'*m*'+'*p*'-Ph), 6.26 (1H,bs,NHcPr), 6.13-6.08 (1H,m,H2'), 5.93-5.88 (1H,m,H3'), 5.58-5.53 (1H,m,H1'), 5.14 (2H,bs,NH_2), 4.28-3.89 (6H,m,CHala,OCH_2, H5'+NHala), 3.17 (1H,t,H4'), 3.04 (1H,bs,CHcPr), 2.87-2.75 (1H,m,lof H6'), 1.74-1.61 (3H,m,1 of H6'+$OCH_2\underline{CH_2}$), 1.43-1.31 (9H,t,CH_3ala+3xCH_2), 0.92-0.85 (5H,m,CH_3+2Hof CH_2cPr), 0.68-0.63 (2H,q,2Hof CH_2cPr).
^{13}C NMR: δ 174.1CO, 160.1 (C2), 156.5 (C4), 151.2 (C6), 151.1 ('*ipso*'-Ph), 136.9 (C2'), 136.0 (C8), 131.4 (C3'), 130.0 ('*m*'-Ph), 125.3 ('*p*'-Ph), 120.5 ('*o*'-Ph), 115.0 (C5), 69.2 (C5'), 66.1 (OCH_2), 59.3 (C1'), 50.7 (CHala), 46.0 (C4'), 34.9 (C6'), 31.7 ($OCH_2\underline{CH_2}$), 28.8 (CH_2-ester), 25.8 (CH_2-ester), 24.2 (CHcPr), 21.9 (CH_2-ester), 21.5 (CH_3ala), 14.4 (CH_3-ester), 7.8 (CH_2cPr).

L-Alanine *cyclo*-hexyl ester hydrochloride salt

$C_9H_{16}N_1O_2Cl_1$, MW=205.71

[0109] This was synthesised according to **Standard Procedure 2**, using L-Alanine (2.0g, 22.5mmol), cyclohexanol (2.34ml, 22.5mmol), *p*-toluene sulfonic acid monohydrate (4.7g, 24.7mmol), and toluene (100ml). The *p*-toluene sulfonate salt was isolated as a pale orange solid (1.45g).

[0110] The reaction was repeated using L-Alanine (3.0g, 33.7mmol), cyclohexanol (5.26ml, 50.6mmol), *p*-toluene sulfonic acid monohydrate (9.62g, 50.6mmol), and toluene (100ml). L-alanine cyclohexyl ester hydrochloride salt was isolated as a white solid (3.15g, 45.45%).
^{1}H NMR (MeOH-d_4): δ 4.90 (1H,m,OCH), 4.12-4.04 (1H,q,CHala), 1.92-1.81 (2H,m,OCH$\underline{CH_2}$), 1.80-1.63 (2H,m, OCH$\underline{CH_2}$), 1.55 (3H,d,J=7.23Hz,CH_3ala), 1.49-133 (6H,m,[$\underline{CH_2}$]$_3$).
^{13}C NMR: δ 169.5 (CO), 75.4 (OCH), 48.9 (CHala), 31.3 (2xCH_2-*o*), 25.2 (2xCH_2-*m*), 23.5 (*p*-CH_2), 15.3 (CH_3ala).

Phenyl-(*c*-hexyloxy-L-alaninyl)-phosphorochloridate

$C_{15}H_{21}N_1O_4P_1Cl_1$, MW=345.79

[0111] This was synthesised according to **Standard Procedure 3**, using L-Alanine c-hexyl ester hydrochloride salt (0.7g, 3.4mmol), $PhOP(O)Cl_2$ (0.51ml, 3.4mmol), triethylamine (0.95ml. 6.8mmol) in DCM (60ml). The usual workup yielded the crude product as a yellow oil (1.12g, 95.2%), which was stored in THF (7ml) to give a 0.46M solution.
^{31}P NMR: δ 9.43, 9.07 (1:1).
^{1}H NMR: δ 7.44-7.33(2H,m,'o'-Ph), 7.32-7.20 (3H,m,'*m*'+'*p*'-Ph), 4.92-4.83 (1H,m,OCH), 4.55-4.42 (1H,m,NHala), 4.28-4.15 (1H,m,CHala), 1.89 (2H,bd,CH_2-'*o*'), 1.76 (1H,bd,CH_2-'*o*'), 1.54 (3H,d,CH_3ala), 1.49-1.32 (6H,m, CH_3CH_2-'*m*'+'*p*').
^{13}C NMR: δ 172.5 (CO), 150.1 ('*ipso*'-Ph), 130.3 ('*m*'-Ph), 126.4 ('*p*'-Ph), 121.0 ('*o*'-Ph), 74.9 (OCH), 51.1 (CHala), 31.8 (CH_2-'*o*'), 25.6 (CH_2-'*p*'), 21.0 (CH_3ala).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-Phenyl-(*c*-hexyloxy-L-alaninyl)-phosphate. Cf1707.

$C_{29}H_{38}N_7O_5P_1$, MW=595.635

[0112] This was synthesised according to **Standard Procedure 4**, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (100mg, 0.35mmol), tBuMgCl (0.7ml, 0.7mmol, of a 1.0M solution in THF), in THF (3ml) and phenyl-(c-hexoxy-L-alaninyl)-phosphorochloridate (2.28ml, 1.05mmol, of a 0.46M solution in THF), at room temperature for 24hrs. The crude product was purified by eluting with 3-4% MeOH in $CHCl_3$, and then 2.5-3.0% MeOH in $CHCl_3$ to give the pure product as a pale yellow foamy solid (199mg, 95.7%).
^{31}P NMR: δ 4.06, 3.99 (1:1).
^{1}H NMR: δ 7.42 (1H,d,J=8.15Hz,H8), 7.23-7.18 (2H,m,'*o*'-Ph), 7.12-7.02 (3H,m,'*m*'+'*p*'-Ph), 6.31 (1H,bs,NHcPr), 5.98 (1H,bs,H2'), 5.78 (1H,bs,H3'), 5.43 (1H,bs,H1'), 5.21 (2H,bs,NH_2), 4.66 (1H,bs,OCH), 4.17-4.02 (3H,m,H5'+NHala), 3.95-3.85 (1H,m,CHala), 3.05-2.94 (2H,m,H4'+CHcPr), 2.73-2.63 (1H,m,1of H6'), 1.69 (2H,bs,CH_2-'*o*'), 1.62-1.53 (2H, m,CH_2-'*o*'), 1.45-1.18 (9H,m,CH_3ala+3xCH_2-'*m*'+'*p*'), 0.76 (2H,d,2Hof CH_2cPr), 0.53 (2H,bs,2Hof CH_2cPr).
^{13}C NMR: δ 172.0CO, 158.4 (C2), 154.8 (C4), 149.7 (C6), 149.6 ('*ipso*'-Ph), 135.5 (C2'), 134.7 (C8), 130.0 (C3'), 128.6 ('*m*'-Ph), 123.8 ('*p*'-Ph), 119.1 ('*o*'-Ph), 113.1 (C5), 72.9 (OCH), 67.8 (C5'), 57.9 (C1'), 59.4 (CHala), 44.7 (C4'), 34.5 (C6'), 30.3 (CH_2-'*o*'), 24.2 (CH_2-'*m*'), 22.8 (CHcPr), 22.5 (CH_2-'*p*'), 20.1 (CH_3ala), 6.4 (CH_2cPr).

MS ES+: m/z 596.2 (100%, M^+), 597.3 (20%, $M+H^+$).
MS FAB: For $C_{29}H_{39}O_5N_7P$ requires 596.2750, found 596.2750.
HPLC: t_R 40.502 (99.8%)-(100% water (0mins) 20% water (35mins), 20% water (45mins), 100% water (55mins)).

L-alanine cyclohexane-methyl ester hydrochloride

$C_{10}H_{20}N_1O_2Cl_1$, MW=221.75

[0113] This was synthesised according to **Standard Procedure 2**, using L-Alanine (3.0g, 33.7 mmol), cyclohexane methanol (4.15ml, 33.7mmol), *p*-toluene sulfonic acid monohydrate (7.05g, 37.1mmol), and toluene (100ml). 9.2g of the the PTSA salt was solubilised in DCM (50ml), and washed with 10% K_2CO_3 (50ml), and water (2x50ml), dried over $MgSO_4$, filtered and the filtrate reduced to dryness to give a yellow oil. This was neutralised with 2M HCl, stirred for 2hrs, and then freeze-dried to give the hydrochloride salt as a white solid (4.32g, 75.8%).
^1H NMR (MeOH-d_4): δ 4.19-4.01 (3H,m,OCH+CHala), 1.79-1.69 (5H,m,CH+*o*-CH_2), 1.58 (3H,d,J=7.21Hz,CH_3ala), 1.37-1.20 (4H,m,*m*-CH_2), 1.09-0.98 (2H,q,*p*-CH_2).
^{13}C NMR: δ 170.1 (CO), 71.3 (OCH_2), 48.9 (CHala), 37.3 (CH), 29.5 (2xCH_2-*o*), 26.4 (*p*-CH_2), 25.7 (2xCH_2-*m*), 15.4 (CH_3ala).

Phenyl-(cyclohexane-methoxy-L-alaninyl)-phosphorochloridate

$C_{16}H_{23}N_1O_4P_1Cl_1$, MW=359.82

[0114] This was synthesised according to **Standard Procedure 3**, using L-Alanine cyclohexane-methyl ester hydrochloride salt (0.7g, 3.16mmol), $PhOP(O)Cl_2$ (0.47ml, 3.16mmol), triethylamine (0.88ml. 6.31mmol) in DCM (70ml). The usual workup yielded the crude product as a yellow oil (1.10g, 96.8%), which was stored in THF (6ml) to give a 0.51M solution.
^{31}P NMR: δ 9.35, 9.05 (1:1).
^1H NMR: δ 4.61-4.50 (1H,q,NHala), 4.28-4.13 (1H,m,CHala), 4.04-4.00 (2H,q,OCH_2), 1.78-1.74 (7H,t,CHcHx+'*o*'-CH_2), 1.57-1.54 (3H,dd,CH_3ala), 1.06-0.96 (2H,q,'*p*'-CH_2).
^{13}C NMR: δ 173.1 (CO), 150.1 ('*ipso*'-Ph), 130.3 ('*m*'-Ph), 126.4 ('*p*'-Ph), 121.0 ('*o*'-Ph), 71.4 (OCH_2), 51.0 (CHala), 37.4 (CHcHx), 29.9 (CH_2-'*o*'), 26.7 (CH_2-'*m*'), 25.9 (CH_2-'*p*'), 21.1 (CH_3ala).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-Phenyl-(*cyclo*hexane-methoxy-L-alaninyl)-phosphate. Cf1708.

$C_{30}H_{40}N_7O_5P_1$, MW=609.66

[0115] This was synthesised according to **Standard Procedure 4**, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (100mg, 0.35mmol), tBuMgCl (0.7ml, 0.7mmol, of a 1.0M solution in THF), in THF (5ml) and phenyl-(*cyclo*hexane-methoxy-L-alaninyl)-phosphorochloridate (2.06ml, 1.05mmol, of a 0.51M solution in THF), at room temperature for 48hrs. The crude product was purified by eluting with 4-6% MeOH in DCM, and then 3% MeOH in $CHCl_3$ to give the pure product as a pale yellow foamy solid (161.1mg, 75.6%).
^{31}P NMR: δ 3.99, 3.92 (1:1).
^1H NMR: δ 7.40 (1H,d,J=7.07Hz,H8), 7.24-7.19 (2H,t,'*o*'-Ph), 7.13-7.03 (3H,m,'*m*'+'*p*'-Ph), 6.00-5.96 (2H,m,H2'+NH-cPr), 5.79 (1H,q,H3'), 5.45 (1H,d,H1'), 5.05 (2H,bs,NH_2), 4.16-4.01 (3H,m,OCH_2+NHala), 3.98-3.88 (1H,m,CHala), 3.86-3.74 (2H,m,H5'), 3.07-3.00 (1H,t,H4'), 2.94 (1H,bs,CHcPr), 2.74-2.63 (1H,m,lof H6'), 1.88-1.50 (7H,m,CH-cHx+2CH2-'*o*'), 1.31-1.27 (3H,t,CH_3ala), 1.21-0.99 (4H,m,2CH_2-'*m*'), 0.89-0.79 (2H,q,CH_2-'*p*'), 0.75 (2H,d,2Hof CH_2cPr), 0.54-0.50 (2H,t,2Hof CH_2cPr).
^{13}C NMR: δ 174.1(CO), 160.2 (C2), 156.4 (C4), 151.2 (C6), 151.1 ('*ipso*'-Ph), 136.7 (C2'), 136.0 (C8), 131.5 (C3'), 130.0 ('*m*'-Ph), 125.2 ('*p*'-Ph), 120.5 ('*o*'-Ph), 115.1 (C5), 71.0 (OCH_2), 69.3 (C5'), 59.3 (C1'), 50.7 (CHala), 46.1 (C4'), 37.4 (CHcHx), 34.9 (C6'), 29.9 (CH_2-'*o*'), 26.6 (CH_2-'*m*'), 25.9 (CH_2-'*p*'), 24.2 (CHcPr), 21.5 (CH_3ala), 7.8 (CH_2cPr).
MS ES+: m/z 610.3 (50%, $M+H^+$), 632.3 (100%, $M+Na^+$), 633.3 ($M+H+Na^+$).
MS FAB: For $C_{30}H_{40}O_5N_7NaP$ requires 632.2726, found 632.2710.
HPLC: t_R 42.859 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).

4-Chlorophenyl-phosphorodichloridate

$C_6H_4O_2P_1Cl_3$, MW=246.43

[0116] Phosphorus oxychloride (2ml, 21.5mmol) was stirred with anhydrous diethylether (70ml) in a 250ml RBF. To this was added, dropwise, a solution of 4-chlorophanol (2.1ml, 21.5mmol), and anhydrous triethylamine (3.0ml, 21.5mmo) in anhydrous diethylether (30ml) at -80°C. This was stirred vigorously at -80°C for lhr and left to rise to room temperature over 16hrs. The triethylamine hydrochloride salt was filtered off, and the filtrate reduced to dryness to give the crude product as a yellow oil (4.61 g, 87.2%).
^{31}P NMR: δ 4.99 (s).
^{13}C NMR: δ 148.4 ('*ipso*'-Ph), 133.2 ('*p*'-Ph), 130.7 ('*m*'-Ph), 122.4 ('*o*'-Ph).

4-Chlorophenyl-(methoxy-L-alaninyl)-phosphorochloridate

$C_{10}H_{12}N_1O_4P_1Cl_2$, MW=246.43

[0117] This was synthesised according to **Standard Procedure 3**, using L-Alanine methyl ester hydrochloride (2.61g, 18.7mmol) and *p*-chlorophenyl phosphorodichloridate (4.61g, 18.7mmol) and triethylamine (5.21ml, 37.4mmol) in anhydrous DCM (100ml). The usual workup yielded the crude product as a colourless crude oil (3.76g, 64.4%) which was stored in anhydrous THF (20ml) to give a 0.6M solution that was used without further purification.
^{31}P NMR: δ 9.48, 9.25 (1:1).
^{1}H NMR: δ 7.36 (2H,d,J=8.20Hz,'*o*'-Ph), 7.32-7.22 (2H,m,'*m*'-Ph), 4.69 (1H,d,NHala), 4.27-4.15 (1H,m,CHala), 3.82 (3H,d,OCH_3), 1.56-1.53 (3H,dd,J=7.04Hz,CH_3ala).
^{13}C NMR: δ 173.4 (CO), 148.6 ('*ipso*'-Ph), 131.9 ('*p*'-Ph), 130.3 ('*m*'-Ph), 122.3 ('*o*'-Ph), 53.2 (OCH_3), 50.9 (CHala), 20.9 (CH_3ala).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[4-chlorophenyl-(methoxy-L-alaninyl)]-phosphate. Cf1620.

$C_{24}H_{29}N_7O_5P_1Cl_1$, MW=562.02

[0118] This was synthesised according to **Standard Procedure 4**, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (250mg, 0.87mmol), tBuMgCl (1.75ml, 1.75mmol of a 1.0M solution in THF), and 4-chlorophenyl-(methoxy-L-alaninyl)-phosphorochloridate (4.37ml, 2.62mmol, of a 0.6M solution in THF), in anhydrous THF (13ml) stirring at room temperature for 24hrs. The crude product was purified by eluting with 3% MeOH in $CHCl_3$ to give the pure product as white foamy solid (364.5mg, 74.5%).
^{31}P NMR: δ 4.01 (s).
^{1}H NMR: δ 7.42 (1H,d,H8), 7.22-7.17 (2H,m,'*m*'-Ph), 7.09-7.03 (2H,t,'*o*'-Ph), 5.99 (1H,d,H2'), 5.93 (1H,s,H3'), 5.83 (1H, bs,NHcPr), 5.45 (1H,bs,H1'), 4.96 (2H,bs,NH_2), 4.11 (2H,bs,H5'), 4.03-3.86 (1H,m,CHala), 3.62 (3H,s,OCH_3), 3.07 (1H,d,J=5.9Hz,H4'), 2.92 (1H,bs,CHcPr), 2.76-2.64 (1H,m,lof H6'), 1.64-1.59 (1H,t,1 of H6'), 1.32-1.26 (3H,q,CH_3ala), 0.76 (2H,d,J=6.40Hz,2H of CH_2cPr), 0.53 (2H,bs,2Hof CH_2cPr).
^{13}C NMR: δ 174.4 (CO), 160.4 (C2), 156.7 (C4), 151.3 (C6), 149.7 ('*ipso*'-Ph), 136.7 (C2'), 135.9 (C8), 131.6 (C3'), 130.5 ('*p*'-Ph), 130.0 ('*m*'-Ph), 121.9 ('*o*'-Ph), 115.2 (C5), 69.4 (C5'), 59.25 (C1'), 52.9(OCH_3), 50.6 (CHala), 46.0 (C4'), 34.9 (C6'), 24.1 (CHcPr), 21.4 (CH_3ala), 7.8 (CH_2cPr).
HPLC: t_R 32.693, 33.012 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).

4-Bromophenyl-phosphorodichloridate

$C_6H_4O_2Cl_2Br_1$, MW=289.87

[0119] This was synthesised by a method analogous to that of 4-chlorophenylphosphorodichloridate, except using: Phosphorus oxychloride (3.29g, 2ml, 21.5mmol), and 4-bromophenol (3.71g, 21.5mmol) in anhydrous diethylether (70ml), and anhydrous triethylamine (2.71g, 3ml, 21.5mmol) in anhydrous diethylether (30ml). The reaction was stirred at -80°C to room temperature for 16hrs. After filtration, and removal of the solvent, the product was obtained as a clear liquid (5.14g, 82.6%).
^{31}P NMR: δ 4.88 (s).
^{1}H NMR: δ 7.63 (2H,d,J=8.14Hz,'*o*'-Ph), 7.28 (2H,t,'*m*'-Ph),

^{13}C NMR: δ 149.0('*ipso*'-Ph), 133.7 ('*m*'-Ph), 122.6 ('*o*'-Ph), 120.9 ('*p*'-Ph).

4-Bromophenyl-(methoxy-L-alaninyl)-phosphorochloridate

$C_{10}H_{12}N_1O_4P_1Cl_1Br_1$, MW=356.55

[0120] This was synthesised according to **Standard Procedure 3,** using L-alanine methyl ester hydrochloride salt (1.0g, 7.16mmol), 4-bromophenyl-phoshorodichloridate (1.82g, 7.16mmol), triethylamine (2ml, 14.3mmol) in DCM (70ml). The usual workup yielded the crude product as a yellow oil (2.24g, 87.7%), which was stored in THF (12ml) to give a 0.524M solution.
^{31}P NMR: δ 9.16, 9.10 (1:1).
^{13}C NMR: δ 173.4(CO), 150.1 ('*ipso*'-*Ph*), 133.3 ('*m*'-Ph), 122.7 ('*o*'-Ph), 119.6 ('*p*'-Ph), 53.3 (OCH_3), 51.0 (CHala), 20.9 (CH_3ala).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[4-bromophenyl-(methoxy-L-alaninyl)]-phosphate. Cf1710.

$C_{24}H_{29}N_7O_5P_1Br_1$, MW=606.42

[0121] This was synthesised according to **Standard Procedure 4,** using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (100mg, 0.35mmol), tBuMgCl (0.7ml, 0.7mmol, of a 1.0M solution in THF), in THF (5ml) and 4-bromophenyl-(methoxy-L-alaninyl)-phosphorochloridate (2.0ml, 1.05mmol, of a 0.524M solution in THF), at room temperature for 24hrs. The crude product was purified by eluting with 4-6% MeOH in DCM, and then in 4% MeOH in DCM, to give the pure product as a white foamy solid (115.2mg, 54.4%).
^{31}P NMR: δ 3.96 (s).
^{1}H NMR: δ 7.42 (1H,d,H8), 7.34-7.30 (2H,dd,J=8.73Hz,'o'-Ph), 7.03-6.97 (2H,t,J=8.68Hz, '*m*'-Ph), 6.02-5.97 (2H,m, H2'+NHcPr), 5.83-5.79 (1H,m,H3'), 5.43 (1H,t,H1'), 5.06 (2H,bs,NH_2), 4.28-4.04 (3H,m,H5'+NHala), 4.02-3.85 (1H,m, CHala), 3.61 (3H,d,OCH_2), 3.05 (1H,d,J=6.09Hz,H4'), 2.94 (1H,d,CHcPr), 2.75-2.66 (1H,m,lof H6'), 1.66-1.56 (1H,m, 1 of H6'), 1.31-1.25 (3H,dd,CH_3ala), 0.79-0.72 (2H,q,2Hof CH_2cPr), 0.54-0.49 (2H,t,2Hof CH_2cPr).
^{13}C NMR: δ 174.4(CO), 160.3 (C2), 156.6 (C4), 151.3 (C6) 150.2 ('*ipso*'-Ph), 136.7 (C2'), 136.0 (C8), 133.0 ('*m*'-Ph), 131.6 (C3'), 122.4 ('*o*'-Ph), 118.1 ('*p*'-Ph), 115.2 (C5), 69.4 (C5'), 59.3 (C1'), 52.9 (OCH_3), 50.6 (CHala), 46.0 (C4'), 34.8 (C6'), 24.2 (CHcPr), 21.3 (CH_3ala), 7.8 (CH_2cPr).
MS ES$^+$: m/z 606.13 (40%, M$^+$), 628.1065 (100%, 79-M+Na$^+$), 630.0967 (95%, 81-M+Na$^+$).
MS FAB: For $C_{24}H_{29}O_5N_7NaPBr$ requires 628.1049, found 628.1058, and $C_{24}H_{29}O_5N_7NaP\,^{81}Br$ requires 630.1028, found 630.1042.
HPLC: t_R 35.882 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).

4-Fluorophenyl-pbosphorodichloridate

$C_6H_4O_2P_1Cl_2F_1$, MW=228.97

[0122] This was synthesised by a method analogous to that of 4-chlorophenylphosphorodichloridate, except using: Phosphorus oxychloride (3.29g, 2ml, 21.5mmol), and 4-fluorophenol (2.41g, 21.5mmol) in anhydrous diethylether (70ml), and anhydrous triethylamine (2.71g, 3ml, 21.5mmol) in anhydrous diethylether (30ml). The reaction was stirred at -80°C for 4hrs, and then at room temperature for 2hrs. After filtration, and removal of the solvent, the product was obtained as a clear liquid (4.08g, 83.0%).
^{31}P NMR: δ 5.50 (s).
^{1}H NMR: δ 7.29-7.24 (2H,m,'*o*'-Ph), 7.09 (2H,t,J=8.29Hz,'*m*'-Ph),
^{13}C NMR: δ 159.7('*ipso*'-Ph), 145.8 ('*m*'-Ph), 122.6 ('o'-Ph), 117.5 ('*p*'-Ph).

4-Fluorophenyl-(methoxy-L-alaninyl)-phosphorochloridate

$C_{10}H_{12}N_1O_4P_1Cl_1F_1$, MW=295.65

[0123] This was synthesised according to **Standard Procedure 3,** using L-alanine methyl ester hydrochloride salt (1.0g, 7.16mmol), 4-fluorophenyl-phoshorodichloridate (1.64g, 7.16mmol), triethylamine (2ml. 14.3mmol) in DCM (70ml). The usual workup yielded the crude product as a yellow oil (1.97g, 93.0%), which was stored in THF (12ml) to give a 0.56M solution.

^{31}P NMR: δ 9.84, 9.60(1:1).
^{1}H NMR: δ 7.32-7.23(2H,m,'*o*'-Ph), 7.12-7.06 (2H,m,'*m*'-Ph), 4.69 (1H,bs,NHala), 4.22 (1H,bs,CHala), 3.82 (3H,d, OCH_3), 1.57-1.53 (3H,m,CH_3ala).
^{13}C NMR: δ 173.5(CO), 161.6 ('*ipso*'-Ph), 145.9 ('*m*'-Ph), 122.5 ('*o*'-Ph), 117.0 ('*p*'-Ph), 53.2 (OCH_3), 50.9 (CHala), 20.9 (CH_3ala).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[4-fluorophenyl-(methoxy-L-alaninyl)]-phosphate. Cf1737.

$C_{24}H_{29}N_7O_5P_1F_1$, MW=545.57

[0124] This was synthesised according to **Standard Procedure 4,** using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (100mg, 0.35mmol), tBuMgCl (0.7ml, 0.7mmol, of a 1.0M solution in THF), in THF (5ml) and 4-fluorophenyl-(methoxy-L-alaninyl)-phosphorochloridate (1.89ml, 1.05mmol, of a 0.56M solution in THF), at room temperature for 24hrs. The solvent was removed under reduced pressure and the residue columned in 2.5-5% methanol in chloroform, and then in 3% methanol in chloroform, to give the pure product as a pale yellow foamy solid (62.0mg, 32.5%).
^{31}P NMR: δ 4.24, 4.23, 4.20, 4.19.
^{1}H NMR: δ 7.52 (1H,d,H8), 7.21-7.14 (2H,m,'*o*'-Ph), 7.03-6.97 (2H,m,'*m*'-Ph), 6.16 (1H,bs,NHcPr), 6.10-6.07 (1H,q, H2'), 5.93-5.89 (1H,q,H3'), 5.44 (1H,d,H1'), 5.14 (2H,bs,NH_2), 4.23-3.98 (4H,m,H5',NHala+CHala), 3.72 (3H,d,OCH_2), 3.16 (1H,d,J=6.03Hz,H4'), 3.03 (1H,d,CHcPr), 2.86-2.74 (1H,m,1 of H6'), 1.76-1.66 (1H,m,1of H6'), 1.42-1.35 (3H,dd, CH_3ala), 0.89-0.83 (2H,q,2H of CH_2cPr), 0.65-0.60 (2H,t,2H of CH_2cPr).
^{13}C NMR: δ 174.4(CO), 161.5 (C2), 160.3+156.6 ('*p*'-Ph), 156.6 (C4), 151.3 (C6) 150.2 ('*ipso*'-Ph), 136.8 (C2'), 136.0 (C8), 131.6 (C3'), 121.9 ('*o*'-Ph), 115.1 (C5), 69.3 (C5'), 59.3 (C1'), 52.9 (OCH_3), 50.6 (CHala), 46.0 (C4'), 34.9 (C6'), 24.2 (CHcPr), 21.3 (CH_3ala), 7.8 (CH_2cPr).
HPLC: t_R 31.536 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).

4-Iodophenyl-phosphorodichloridate

$C_6H_4O_2P_1Cl_2I_1$, MW=336.07

[0125] This was synthesised by a method analogous to that of 4-chlorophenylphosphorodichloridate, except using: Phosphorus oxychloride (3.29g, 2ml, 21.5mmol), and 4-iodophenol (4.72g, 21.5mmol) in anhydrous diethylether (60ml), and anhydrous triethylamine (2.71g, 3ml, 21.5mmol) in anhydrous diethylether (20ml). The reaction was stirred at -80°C for 4hrs, and then at room temperature for 2hrs. After filtration, and removal of the solvent, the product was obtained as a clear liquid (6.2g, 85.8%).
^{31}P NMR: δ 4.72 (s).
^{1}H NMR: δ 7.71 (2H,d,J=8.59Hz,'*o*'-Ph), 7.06-7.02 (2H,dd,3=8.80Hz,'*m*'-Ph),
^{13}C NMR: δ 149.9('*ipso*'-Ph), 139.8 ('*m*'-Ph), 122.9 ('*o*'-Ph), 91.9 ('*p*'-Ph).

4-Iodophenyl-(methoxy-L-alaninyl)-phosphorochloridate

$C_{10}H_{12}N_1O_4P_1Cl_1I_1$, MW=403.55

[0126] This was synthesised according to **Standard Procedure 3,** using L-alanine methyl ester hydrochloride salt (1.0g, 7.16mmol), 4-iodophenyl-phoshorodichloridate (2.41g, 7.16mmol), triethylamine (2ml. 14.3mmol) in DCM (70ml). The usual workup yielded the crude product as a yellow oil (3.59g, >100%), which was stored in THF (14ml) to give a 0.51M solution.
^{31}P NMR: δ 9.31, 9.08 (1:1).
^{1}H NMR: 7.74-7.69(2H,m,'*o*'-Ph), 7.32-7.05 (2H,m,'*m*'-Ph), 4.73 (1H,bs,NHala), 4.20 (1H,bs,CHala), 3.81 (3H,d, OCH_3), 1.56-1.53 (3H,dd,J=7.06Hz,CH_3ala).
^{13}C NMR: δ 173.4(CO), 149.9 ('*ipso*'-Ph), 139.5 ('*m*'-Ph), 123.0 ('*o*'-Ph), 90.4 ('*p*'-Ph), 53.3 (OCH_3), 50.9 (CHala), 20.9 (CH_3ala).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[4-iodophenyl-(methoxy-L-alaninyl)]-phosphate. Cf1738.

$C_{24}H_{29}N_7O_5P_1I_1$, MW=653.48

[0127] This was synthesised according to **Standard Procedure 4**, using (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (100mg, 0.35mmol), tBuMgCl (0.7ml, 0.7mmol, of a 1.0M solution in THF), in THF (5ml) and 4-iodophenyl-(methoxy-L-alaninyl)-phosphorochloridate (2.05ml, 1.05mmol, of a 0.51M solution in THE), at room temperature for 48hrs. The solvent was removed under reduced pressure and the residue columned in 3-6% methanol in chloroform, and then in 3% methanol in chloroform, to give the pure product as a white foamy solid (82.0mg, 29.9%).

^{31}P NMR: δ 3.92 (s).

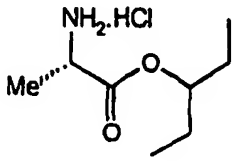
^{1}H NMR: δ 7.63-7.59 (2H,dd,J=8.65Hz,'*m*'-Ph), 6.98 (2H,t,J=8.20Hz'*o*'-Ph), 6.25 (1H,bs,NHcPr), 6.09 (1H,t,H2'), 5.91 (1H,t,H3'), 5.54 (1H,d,H1'), 5.21 (2H,bs,NH_2), 4.35-4.16 (3H,m,H5',NHala), 4.07-3.95 (1H,m,CHala), 3.71 (3H,d, OCH_3ala), 3.15 (1H,d,J=7.23Hz,H4'), 3.03 (1H,bs,CHcPr), 2.85-2.74 (1H,m,1of H6'), 1.76-1.65 (1H,m,1of H6'), 1.43-1.35 (3H,t,CH_3ala), 0.89-0.83 (2H,q,2Hof CH_2cPr), 0.63 (2H,bs,2Hof CH_2cPr).

^{13}C NMR: δ 174.4(CO) 160.2 (C2), 156.5 (C4), 151.1 (C6) 151.0 ('*ipso*'-Ph), 139.0 (C2'), 136.8 ('*m*'-Ph), 136.0 (C8), 131.5 (C3'), 122.8 ('*o*'-Ph), 115.0 (C5), 88.9 ('*p*'-Ph), 69.4 (C5'), 59.3 (C1'), 52.9 (OCH_3), 50.6 (CHala), 46.0 (C4'), 34.8 (C6'), 24.2 (CHcPr), 21.3 (CH_3ala), 7.8 (CH_2cPr).

HPLC: t_R 33.848 (100%)-(100% water (0mins), 20% water (35mins), 20% water (45mins), 100% water (55mins)).

L-Alanine (3-pentyl) ester hydrochloride salt

[0128]

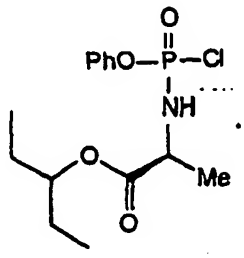


[0129] Thionyl chloride (1.6 ml, 0.022 M) was added dropwise to a stirred solution of 3-pentanol (18.2 ml, 0.17 M) at 0 °C under nitrogen. The mixture was stirred for 30 minutes, then allowed to warm to room temperature. L-Alanine (pre-dried at 60 °C over P_2O_5 for 4 hrs: 1.0 g, 0.011 M) was added and the resulting suspension was heated at reflux overnight (the reaction mixture became a clear, colourless solution). The solvent was removed under reduced pressure to leave an oil which was repeatedly triturated and coevaporated with diethyl ether, then petrol (60/80) to remove traces of 3-pentanol. The resulting oily residue solidified on drying under high vacuum to give a peach-coloured solid (1.96 g, 10 mmol, 89 %).

δ_H (d_4-CH_3OH, 300 MHz) 0.94 (t, 6H, O-CH(CH_2CH_3)$_2$, *J* = 7), 1.57 (d, 3H, CH_3-ala, *J*= 7), 1.67 (m, 4H, O-CH (CH_2CH_3)$_2$, *J* = 7), 4.12 (q, 1H, CH-ala, *J* = 7), 4.88 [m, 1H, O-CH(C_2H_2)$_2$]; δ_C (d_4-CH_3OH, 75 MHz) 8.87 [O-CH (CH_2CH_3)$_2$], 15.38 (CH_3-ala), 26.39, 26.44 [O-CH(CH_2CH_3)$_2$], 48.82 (CH-ala), 79.88 [O-CH(C_2H_5)$_2$], 170.03 (C=O).

Phenyl(3-pentyloxy-L-alaninyl)phosphorochloridate

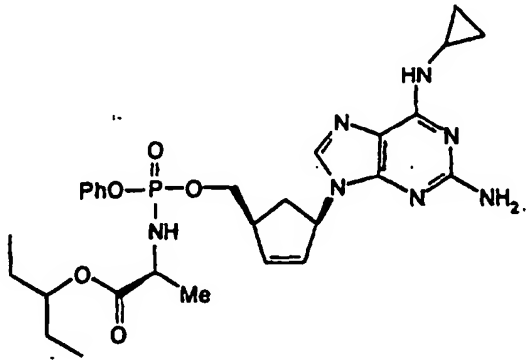
[0130]



[0131] Prepared according to **Standard Procedure 3,** from phenyl dichlorophosphate (0.45 ml, 3.0 mmol), dry triethylamine (0.8 ml, 6.0 mmol), L-alanine (3-pentyl) ester hydrochloride salt 1a (0.583 g, 3.0 mmol) and dry DCM (60 ml total). The crude product was obtained as a clear, pale yellow oil (1.055 g, >100 %).
δ_P ($CDCl_3$, 121 MHz) 8.99, 9.37
[0132] The product was redissolved in dry THF (5 ml) and used as a 0.211 g/ml solution.

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl(3-pentyloxy-L-alaninyl)phosphate [Cf 1685]

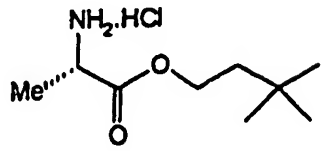
[0133]



[0134] Prepared according to **Standard Procedure 4,** from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), 'BuMgCl (1.0 M in THE: 1.4 ml, 1.4 mmol), phenyl(3-pentyloxy-L-alaninyl) phosphor-ochloridate **1b** (3.3 ml of 0.211 g/ml solution, 2.1 mmol) and dry THE (8 ml). TLC (8 % MeOH in $CHCl_3$) showed the reaction to be complete after 1.5 hrs. The crude residue was purified twice by column chromatography, using (i) MeOH:$CHCl_3$ (4:96) and (ii) MeOH:$CHCl_3$ (3:97) as eluent, to give the product as a clear, colourless oil, which solidified to a white foam after trituration and coevaporation with diethyl ether (0.202 g, 0.35 mmol, 50 %). δ_P ($CDCl_3$, 121 MHz) 3.89; δ_H ($CDCl_3$, 300 MHz) 0.66 (m, 2H, CH_2-cPr), 0.90 [m, 8H, CH_2-cPr and $CH(CH_2CH_3)_2$], 1.43 (m, 3H, CH_3-ala), 1.58 [m, 4H, $CH(CH_2CH_3)_2$], 1.72 (m, 1H, 6'H_a), 2.82 (m, 1H, 6'H_b), 3.05 (m, 1H, CH-cPr), 3.20 (m, 1H, 4'H), 3.77 (m, 1H, CH-ala), 4.05 (m, 1H, NH-ala), 4.22 (m, 2H, 5'H), 4.80 (m, 1H, O-CH-), 4.89 (bs, 2H, NH_2), 5.56 (m, 1H, 1'H), 5.78 (bs, 1H, NH-cPr), 5.93 (m, 1H, 3'H), 6.12 (m, 1H, 2'H), 7.26 (m, 5H, ArH), 7.51 (d, 1H, 8H); δ_C ($CDCl_3$, 75 MHz) 6.37 (CH_2-cPr), 8.50 [$CH(CH_2CH_3)_2$], 20.28 (CH_3-ala), 22.68 (CH-cPr), 25.28, 25.38 [$CH(CH_2CH_3)_2$], 33.51, 33.60 (6'C), 44.59, 44.69 (4'C), 49.40 (CH-ala), 57.79, 57.83 (1'C), 67.90 (5'C), 77.29 (OCH), 113.86 (5C), 119.10-119.18 (*o*-Ph), 123.84 (*p*-Ph), 128.61 (*m*-Ph), 130.09, 130.16 (3'C), 134.45, 134.56 (8C), 135.27, 135.41 (2'C), 149.66-149.93 (6C and *Ipso*-Ph), 155.26 (4C), 158.95 (2C), 172.32, 172.44 (C=O); ***m/z*** (FAB) 584.2751 (MH^+, $C_{28}H_{39}N_7O_5P$ requires 584.2750).

L-Alanine (3,3-dimethyl-1-butyl) ester hydrochloride salt

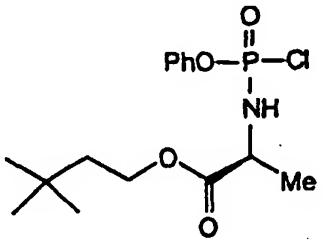
[0135]



[0136] Prepared according to **Standard Procedure 2**, from L-alanine (1.6 g, 18 mmol), *p*-TSA monohydrate (3.8 g, 20 mmol), 3,3-dimethyl butan-1-ol (2.2 ml, 18 mmol) and toluene (100 ml). Conversion to the hydrochloride salt: the *p*-toluene sulfonate salt was redissolved in $CHCl_3$ and washed with 10 % potassium carbonate solution and water. The organic layer was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure to give the crude product as an oil. Aq. HCl (1 M), was added and the solution stirred for 30 minutes at room temperature. The solution was freeze-dried to give the hydrochloride salt as a white solid (3.31 g, 15.8 mmol, 88 %).
δ_H (d_4-CH_3OH, 300 MHz) 0.93 [s, 9H, O-$(CH_2)_2(CH_3)_3$], 1.50 (d, 3H, CH_3-ala, J = 7), 1.59 (t, 2H, O-CH_2CH_2, J = 7), 4.05 (q, 1H, CH-ala, J = 7), *4.25* (m, 2H, O-CH_2); δ_c (d_4-CH_3OH, 75 MHz) 15.18 (CH_3-ala), 28.91 [$C(CH_3)_3$], 29.54 [C $(CH_3)_3$], 41.62 (O-CH_2CH_2-), 48.85 (CH-ala), 64.11 (O-CH_2CH_2-), 170.03 (C=O).

Phenyl(3,3-dimethyl-1-butoxy-L-alaninyl)phosphorochloridate

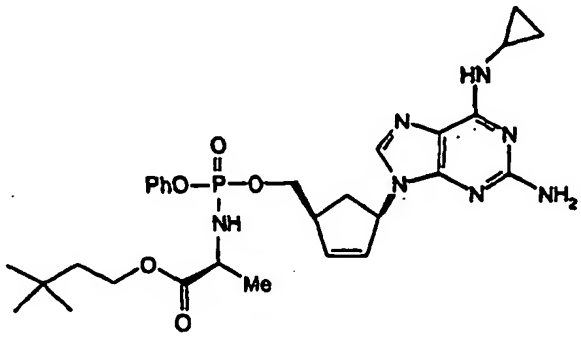
[0137]



[0138] Prepared according to **Standard Procedure 3**, from phenyl dichlorophosphate (0.45 ml, 3.0 mmol), dry triethylamine (0.8 ml, 6.0 mmol), L-alanine (3,3-dimethyl-1-butyl) ester hydro-chloride salt **2a** (0.632 g, 3.0 mmol) and dry DCM (60 ml total). The crude product was obtained as a clear, pale yellow oil (1.038 g, 99 %).
δ_P ($CDCl_3$, 121 MHz) 8.94, 9.30
[0139] The product was redissolved in dry THE (5 ml) and used as a 0.208 g/ml solution.

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl(3,3-dimethyl-1-butoxy-L-alaninyl)phosphate [Cf 1687]

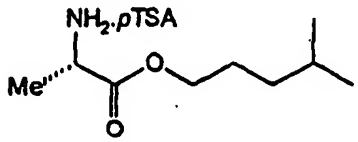
[0140]



[0141] Prepared according to **Standard Procedure 4**, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), ^{t}BuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol), phenyl (3,3-dimethyl-1-butoxy-L-alaninyl) phosphorochloridate **2b** (3.5 ml of 0.208 g/ml solution, 2.1 mmol) and dry THE (8 ml). TLC (8 % MeOH in $CHCl_3$) showed the reaction to be complete after 1.5 hrs. The crude residue was purified twice by column chromatography, using MeOH:$CHCl_3$ (4:96) as eluent, to give the product as a clear, colourless oil, which solidified to a white foam after trituration and coevaporation with diethyl ether (0.287 g, 0.5 mmol, 69 %).
δ_P ($CDCl_3$, 121 MHz) 3.83; δ_H ($CDCl_3$, 300 MHz) 0.66 (m, 2H, CH_2-cPr), 0.90 (m, 2H, CH_2-cPr), 0.97 [s, 9H, C(CH_3)$_3$] 1.41 (m, 3H, CH_3-ala), 1.57 (m, 2H, O-CH_2CH_2), 1.74 (m, 1H, 6'H_a), 2.82 (m, 1H, 6'H_b), 3.05 (m, 1H, CH-cPr), 3.20 (m, 1H, 4'**H**), 3.70 (m, 1H, CH-ala), 4.04 (m, 1H, NH-ala), 4.22 (m, 4H, 5'**H** and O-CH_2CH_2), 4.88 (bs, 2H, NH_2), 5.57 (m, 1H, 1'**H**), 5.75 (bs, 1H, NH-cPr), 5.93 (m, 1H, 3'**H**), 6.12 (m, 1H, 2'**H**), 7.27 (m, 5H, Ar**H**), 7.52 (d, 1H, 8**H**); δ_C ($CDCl_3$, 75 MHz) 6.35 (CH_2-cPr), 19.95, 20.01 (CH_3-ala), 22.69 (CH-cPr), 28.52 [C(CH_3)$_3$], 28.52 [C(CH_3)$_3$], 33.49, 33.57 (6'**C**), 40.59, 40.63 (OCH_2CH_2-), 44.58, 44.68 (4'**C**), 49.28 (CH-ala), 57.79, 57.83 (1'**C**), 62.28, 62.31 (OCH_2CH_2-), 67.86, 67.94 (5'**C**), 113.81 (SC), 119.10, 119.16 (*p*-Ph), 123.84 (*o*-Ph), 128.61 (*m*-Ph), 130.10, 130.16 (3'**C**), 134.47, 134.56 (8**C**), 135.29, 135.40 (2'**C**), 149.67-149.75 (6**C** and *ipso*-Ph), 155.25 (4**C**), 158.96 (2**C**), 172.55, 172.65 (C=O); ***m/z*** (FAB) 598.2896 (MH^+, $C_{29}H_{41}N_7O_5P$ requires 598.2907).

L-Alanine (4-methyl-1-pentyl) ester p-toluene sulfonate salt

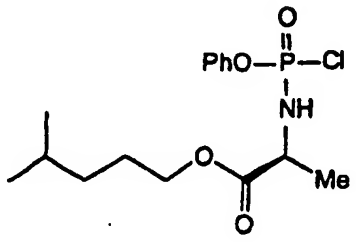
[0142]



[0143] Prepared according to **Standard Procedure 2**, from L-alanine (1.6 g, 18 mmol), *p*-TSA monohydrate (3.8 g, 20 mmol), 4-methyl pentan-1-ol (2.24 ml, 18 mmol) and toluene (100 ml). The *p*-toluene sulfonate salt was isolated as a white solid (6.082 g, 17.6 mmol, 98 %). δ_H (d_4-CH_3OH, 300 MHz) 0.93 [d, 6H, CH(CH_3)$_2$], 127 (m, 2H, O-$CH_2CH_2CH_2$-), 1.54 (d, 3H, CH_3-ala), 1.59 [m, 1H, CH(CH_3)$_2$], 1.69 [m, 2H, O-(CH_2)$_2$$CH_2$], 2.39 (s, 3H, CH_3, *p*-TSA), 4.10 (m, 1H, CH-ala), 4.24 (m, 2H, O-CH_2), 7.25 (d, 2H, Ar**H**, *p*-TSA), 7.72 (d, 2H, Ar**H**, *p*-TSA); δ_C (d_4-CH_3OH, 75 MHz) 15.23 (CH_3-ala), 20.31 (CH_3-*p*TSA), 21.83 [CH(CH_3)$_2$],, 26.45 (O-$CH_2CH_2CH_2$-), 27.87 [CH(CH_3)$_2$], 34.93 (O-$CH_2CH_2CH_2$-), 48.85 (CH-ala), 66.77 [O-CH_2(CH_2)$_2$], 125.93 (*o*-Ph, *p*-TSA), 128.83 (*m*-Ph, *p*-TSA), 140.75 (*ipso*-C-CH_3, *p*-TSA), 142.39 (*Ipso*-C-S,*p*-TSA), 170.07 (C=O).

Phenyl(4-methyl-1-pentyloxy-L-alaninyl)phosphorochloridate

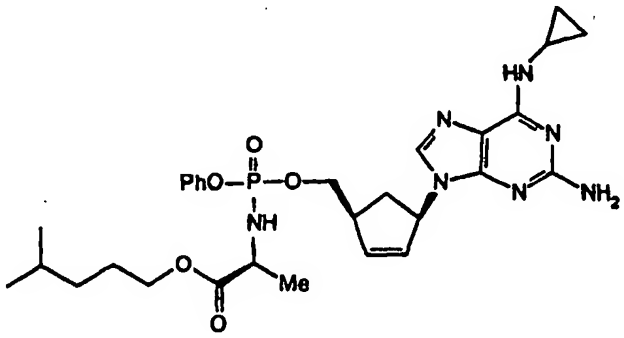
[0144]



[0145] Prepared according to **Standard Procedure 3**, from phenyl dichlorophosphate (0.9 ml, 6.0 mmol), dry triethylamine (1.7 ml, 12.0 mmol), L-alanine (4-methyl-1-pentyl) ester *p*-toluene sulfonate salt **3a** (2.081 g, 6.0 mmol) and dry DCM (100 ml total). The crude product was obtained as a clear, colourless oil (1.79 g, 85 %).
δ_P ($CDCl_3$, 121 MHz) 8.95, 9.31
[0146] The product was redissolved in dry THF (10 ml) and used as a 0.179 g/ml solution.

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl (4-methyl-1-pentyloxy-L-alaninyl)phosphate [Cf1721]

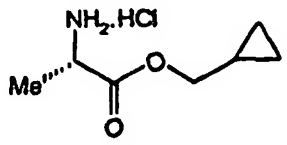
[0147]



[0148] Prepared according to **Standard Procedure 4**, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), ^{t}BuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol), phenyl(4-methyl-1-pentyloxy-L-alaninyl)phosphorochloridate **3b** (4.1 ml of 0.179 g/ml solution, 2.1 mmol) and dry THF (10 ml). TLC (8 % MeOH in $CHCl_3$) showed the reaction to be complete after 3 hrs. The crude residue was purified by column chromatography, using MeOH:$CHCl_3$ (4:96) as eluent, to give the product as a clear, colourless oil, which solidified to a white foam after trituration and coevaporation with diethyl ether (0.288 g, 0.5 mmol, 69 %).
δ_P ($CDCl_3$, 121 MHz) 3.84, 3.88; δ_H ($CDCl_3$, 300 MHz) 0.64 (m, 2H, CH_2-cPr), 0.87 (m, 2H, CH_2-cPr), 1.24 [m, 2H, CH(CH_3)$_2$], 1.40 (t, 3H, CH_3-ala), 1.60 [m, 3H, CH(CH_3)CH_3], 1.73 [m, 3H, CH(CH_3)CH_3], 2.19 (m, 1H, 6'H_a), 2.80 (m, 1H, 6'H_b), 3.03 (m, 1H, CH-cPr), 3.18 (m, 1H, 4'H), 3.88 (m, 1H, CH-ala), 4.03 (m, 3H, OCH_2- and NH -ala), 4.21 (m, 2H, 5'H), 4.99 (bs, 2H, NH_2), 5.55 (m, 1H, 1'H), 5.91 (m, 2H, NH-cPr and 3'H), 6.10 (m, 1H, 2'H), 7.29 (m, 5H, ArH), 7.51 (d, 1H, 8H); δ_C ($CDCl_3$, 75 MHz) 7.79 (CH_2-cPr), 21.55 (CH_3-ala), 21.61 [CH(CH_3)$_2$], 23.69 (CH-cPr), 25.66 (O-$CH_2CH_2CH_2$-), 29.63 [CH(CH_3)$_2$], 35.00 (6'C), 38.81 (O-$CH_2CH_2CH_2$-), 46.01, 46.11 (4'C), 50.72 (CH-ala), 59.21 (1'C), 69.31 (5'C), 69.85 (O-CH_2CH_2-), 115.25 (5C), 120.52-120.62 (*p*-Ph), 125.25 (*o*-Ph), 130.04 (*m*-Ph), 131.59 (3'C), 135.98 (8C), 136.71, 136.79 (2'C), 151.08, 151.17 (6C and *ipso*-Ph), 156.70 (4C), 160.40 (2C), 174.00, 174.10 (C=O); ***m/z*** (FAB) 598.2883 (MH^+, $C_{29}H_{41}N_7O_5P$ requires 598.2907).

L-Alanine (cyclopropyl methyl) ester hydrochloride salt

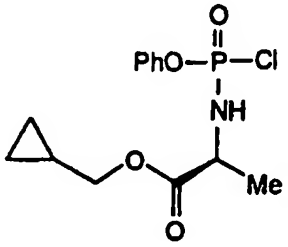
[0149]



[0150] Thionyl chloride (1.2 ml, 0.017 M) was added dropwise to a stirred solution of cyclopropyl methanol (6.8 ml, 8.4 mmol) at 0 °C under nitrogen. The mixture was stirred for 30 minutes, then allowed to warm to room temperature. L-Alanine (pre-dried at 60 °C over P_2O_5 for 4 hrs: 0.75 g, 8.4 mmol) was added and the resulting suspension was heated at reflux overnight (the reaction mixture became a clear, colourless solution). The solvent was removed under reduced pressure to leave an orange/red oil which was repeatedly triturated and coevaporated with diethyl ether, to remove traces of cyclopropyl methanol. Diethyl ether (~200 ml) was added and the mixture was stirred for 30 min. The resulting suspension was filtered to give the product as a cream solid (1.29 g, 7.1 mmol, 85 %). δ_H (d_4-CH_3OH, 300 MHz) 0.38 (m, 2H, CH_2-cPr), 0.65 (m, 2H, CH_2-cPr), 1.24 (m, 1H, CH-cPr), 1.60 (d, 3H, CH_3-ala, $J = 7$), 4.13 (m, 3H, CH-ala and O-CH_2); δ_C (d_4-CH_3OH, 75 MHz) 4.17 (CH_2-cPr), 10.98 (CH-cPr), 16.72 (CH_3-ala), 50.33 (CH-ala), 72.70 (O-CH_2), 171.56 (C=O).

Phenyl(cyclopropyl methoxy-L-alaninyl)phosphorochloridate

[0151]

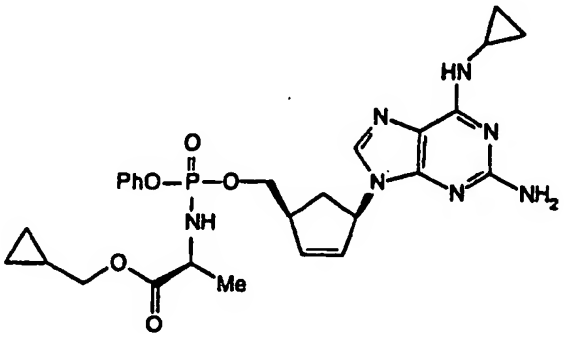


[0152] Prepared according to **Standard Procedure 3**, from phenyl dichlorophosphate (0.9 ml, 6.0 mmol), dry triethylamine (1.7 ml, 12.0 mmol), L-alanine (cyclopropyl methyl) ester *p*-toluene sulfonate salt **4a** (1.082 g, 6.0 mmol) and dry DCM (100 ml total). The crude product was obtained as a clear, yellow oil (1.79 g, 94 %).
δ_P ($CDCl_3$, 121 MHz) 9.00, 9.36
[0153] The product was redissolved in dry THF (5 ml) and used as a 0.385 g/ml solution.

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopeatene-1-methanol O-[phenyl(cyclopropyl methoxy-L-alaninyl)]phosphate

[Cf 1774]

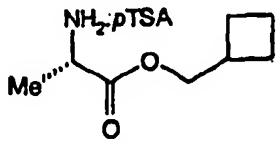
[0154]



[0155] Prepared according to **Standard Procedure 4**, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), 'BuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol) phenyl(cyclopropyl meth-oxy-L-alaninyl) phosphorochloridate **4b** (1.85 ml of 0.385 g/ml solution, 2.1 mmol) and dry THF (8 ml). TLC (8 % MeOH in $CHCl_3$) showed the reaction to be complete after 3.5 hrs. The crude residue was purified twice by column chromatography, using MeOH:$CHCl_3$ (4:96) as eluent, to give the product as a clear, colourless oil, which solidified to a white foam after trituration and coevaporation with diethyl ether (0.244 g, 0.4 mmol, 61 %).
δ_P ($CDCl_3$, 121 MHz) 3.88, 3.94; δ_H ($CDCl_3$, 300 MHz) 0.29 (m, 2H, CH_2-cPr), 0.61 (m, 2H, CH_2-cPr), 0.87 (m, 2H, CH_2-cPr), 1.17 (m, 1H, CH-cPr), 1.42 (t, 3H, CH_3-ala), 1.69 (m, 1H, 6'H_a), 2.81 (m, 1H, 6'H_b), 3.04 (m, 1H, CH-cPr), 3.18 (m, 1H, 4'H), 4.01 (m, 4H, OCH_2-, CH-ala and NH-ala), 4.21 (m, 2H, 5'H), 5.03 (bs, 2H, NH_2), 5.56 (m, 1H, 1'H), 5.91 (m, 1H, 3'H), 6.05 (bs, 1H, NH-cPr), 6.10 (m, 1H, 2'H), 725 (m, 5H, ArH), 7.51 (d, 1H, 8H); δ_C ($CDCl_3$, 75 MHz) 2.24 (CH_2-cPr), 6.33 (CH_2-cPr), 8.66 (CH_2-cPr), 20.05, 20.11 (CH_3-ala), 22.68 (CH-cPr), 33.55 (6'C), 44.58, 44.68 (4'C), 49.24, 49.31 (CH-ala), 57.77, 57.82 (1'C), 67.76, 67.93 (O-CH_2), 69.27, 69.29 (5'C), 113.74 (5C), 119.10-119.19 (*p*-Ph), 123.84 (*o*-Ph), 128.61 (*m*-Ph), 130.09, 130.13 (3'C), 134.42, 134.50 (8C), 135.32, 135.40 (2'C), 149.66, 149.74 (6C and *ipso*-Ph), 155.26 (4C), 159.00 (2C), 172.64, 172.73 (C=O).

L-Alanine (cyclobutyl methyl) ester hydrochloride salt

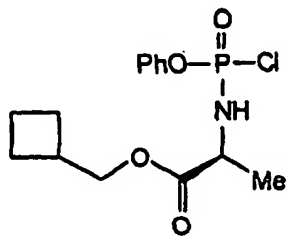
[0156]



[0157] Prepared according to **Standard Procedure 2**, from L-alanine (1.6 g, 18 mmol), *p*-TSA monohydrate (3.8 g, 20 mmol), cyclobutane methanol (1.9 ml, 20 mmol) and toluene (100 ml). The *p*-toluene sulfonate salt was isolated as a white solid (4.249 g, 12.9 mmol, 72 %). δ_H (d_4-CH_3OH, 300 MHz) 1.54 (d, 3H, CH_3-ala, J= 7), 1.89 (m, 4H, cBu-2/4H), 2.08 (m, 2H, cBu-3H), 2.39 (s, 3H, CH_3, *p*-TSA), 2.69 9m, 1H, CH-cBu), 4.11 (q, 1H, CH-ala, J = 7), 4.22 (m, 2H, O-CH_2), 726 (d, 2H, ArH, *p*-TSA), 7.73 (d, 2H, ArH, *p*-TSA); δ_C (d_4-CH_3OH, 75 MHz) 16.7 (CH_3-ala), 19.6 (CH_2-cBu), 21.7 (CH_3-*p*TSA), 25.9 (CH_2-cBu), 35.7 (CH-cBu), 48.9 (CH-ala), 71.3 (O-CH_2), 127.4 (*o*-Ph, *p*-TSA), 130. 3 (*m*-Ph, *p*-TSA), 142.2 (*ipso*-C-CH_3, *p*-TSA), 143.8 (*ipso*-C-S, *p*-TSA), 171.6 (C=O).

Phenyl(cyclobutyl methoxy-L-alaninyl)phosphorochloridate

[0158]

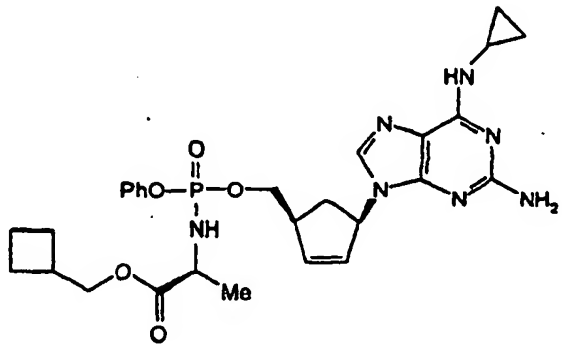


[0159] Prepared according to **Standard Procedure 3**, from phenyl dichlorophosphate (0.9 ml, 6.0 mmol), dry triethylamine (1.7 ml, 12.0 mmol), L-alanine (cyclobutyl methyl) ester *p*-toluene sulfonate salt **5a** (1.98 g, 6.0 mmol) and dry DCM (100 ml total). The crude product was obtained as a clear, colourless oil (2.04 g, >100 %).
δ_P ($CDCl_3$, 121 MHz) 9.00, 9.34
[0160] The product was redissolved in dry THF (5 ml) and used as a 0.408 g/ml solution.

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl(cyclobutyl methoxy-L-alaninyl)]phosphate

[Cf 1773]

[0161]

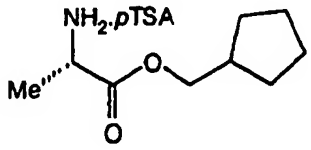


[0162] Prepared according to **Standard Procedure 4**, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), ^{t}BuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol) phenyl(cyclobutyl meth-oxy-L-alaninyl) phosphorochloridate **5b** (1.7 ml of 0.408 g/ml solution, 2.1 mmol) and dry THF (8 ml). TLC (8 % MeOH in $CHCl_3$) showed the reaction to be complete after 3 hrs. The crude residue was purified twice by column chromatography, using MeOH:$CHCl_3$ (4:96) as eluent, to give the product as a clear, colourless oil, which solidified to a white foam after trituration and coevaporation with diethyl ether (0.213 g, 0.4 mmol, 52 %).
δ_P ($CDCl_3$, 121 MHz) 3.87, 3.91; δ_H ($CDCl_3$, 300 MHz) 0.65 (m, 2H, C**H**$_2$-cPr), 0.89 (m, 2H, C**H**$_2$-cPr), 1.41 (t, 3H, C**H**$_3$-ala), 1.74 (m, 3H, C**H**$_2$-cBu and 6'**H**$_a$), 2.06 (m, 2H, C**H**$_2$-cBu), 2.61 (m, 2H, C**H**$_2$-cBu), 2.81 (m, 1H, 6'**H**$_b$), 3.04 (m, 1H, C**H**-cPr), 3.19 (m, 1H, 4'**H**), 3.90 (m, 1H, NH-ala), 4.09 (m, 3H, OC**H**$_2$-, and C**H**-ala), 4.22 (m, 2H, 5'**H**), 4.98 (bs, 2H, N**H**$_2$), 5.56 (m, 1H, 1'**H**), 5.92 (m, 2H, 3'**H** and NH-cPr), 6.11 (m, 1H, 2'**H**), 7.26 (m, 5H, Ar**H**), 7.52 (d, 1H, 8**H**); δ_C ($CDCl_3$, 75 MHz) 6.37 (**C**H$_2$-cPr), 17.33 (**C**H$_2$-cBu), 20.17, 20.23 (**C**H$_3$-ala), 22.68 (**C**H-cPr), 23.57 (2 × **C**H$_2$-cBu), 32.86 (**C**H-cBu), 33.51, 33.55 (6'**C**), 44.58, 44.68 (4'**C**), 49.23, 49.28 (**C**H-ala), 57.81, 57.85 (1'**C**), 67.78-67.94 (5'C), 68.17, 68.20 (O-**C**H$_2$), 113.83 (SC), 119.09-119.19 (*p*-Ph), 123.87 (o-Ph), 128.62 (*m*-Ph), 130.11, 130.15 (3'**C**), 134.51,

134.61 (8C), 135.30, 135.39 (2'C), 149.64-149.97 (6C and *ipso*-Ph), 155.20 (4C), 158.87 (2C), 172.64, 172.74 (C=O).

L-Alanine (cyclopentyl methyl) ester p-toluene sulfonate salt

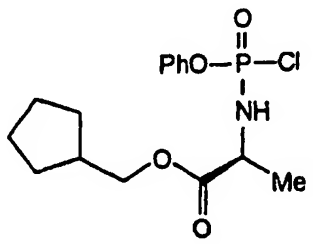
[0163]



[0164] Prepared according to **Standard Procedure 2**, from L-alanine (1.6 g, 18 mmol), *p*-TSA monohydrate (3.8 g, 20 mmol), cyclopentane methanol (1.9 ml, 18 mmol) and toluene (100 ml). The *p*-toluene sulfonate salt was isolated as a white solid (6.21 g, 18 mmol, 100 %). δ_H (d_4-CH_3OH, 300 MHz) 1.22 (m, 2H, cPent 2/5H_a), 1.46 (d, 3H, CH_3-ala), 1.56 (m, 4H, cPent 2/3/4/5H_b), 1.70 (m, 2H, cPent 3/4H_a), 2.19 (m, 1H, CH-cPent), 2.31 (s, 3H, CH_3, *p*-TSA), 4.06 (m, 3H, O-CH_2 and CH-ala), 7.18 (d, 2H, ArH, *p*-TSA), 7.64 (d, 2H, ArH, *p*-TSA); δ_C (d_4-CH_3OH, 75 MHz) 15.25 (CH_3-ala), 20.30 (CH_3, *p*-TSA), 25.27 (CH_2-cPent), 29.10, 29.15 (CH_2-cPent), 38.72 (CH-cPent), 48.84 (CH-ala), 70.12 (O-CH_2), 125.93 (*o*-Ph, *p*-TSA), 128.82 (*m*-Ph, *p*-TSA), 140.75 (*ipso*-C-CH_3, *p*-TSA), 142.40 (*ipso*-C-S, *p*-TSA), 170.09 (C=O).

Phenyl(cyclopentyl methoxy-L-alaninyl)phosphorochloridate

[0165]

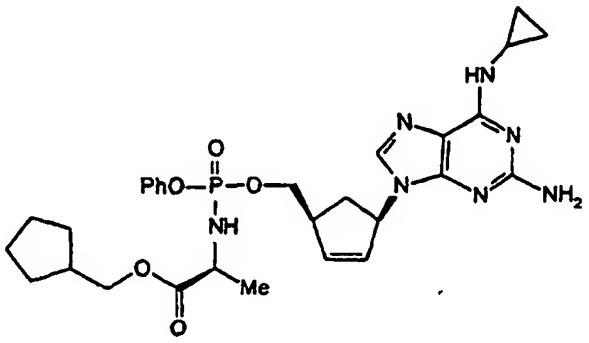


[0166] Prepared according to **Standard Procedure 3**, from phenyl dichlorophosphate (0.9 ml, 6.0 mmol), dry triethylamine (1.7 ml, 12.0 mmol), L-alanine (cyclopentane methyl) ester *p*-toluene sulfonate salt 6a (2.069 g, 6.0 mmol) and dry DCM (100 ml total). The crude product was obtained as a clear, yellow oil (1.97 g, 95 %).
δ_P ($CDCl_3$, 121 MHz) 8.94, 9.30

[0167] The product was redissolved in dry THF (10 ml) and used as a 0.197 g/ml solution.

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl(cyclopentyl methoxy-L-alaninyl)phosphate [Cf 1722]

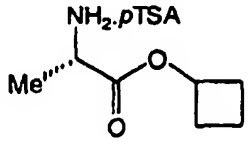
[0168]



[0169] Prepared according to **Standard Procedure 4**, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), ^{t}BuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol), phenyl (cyclopen-tane methoxy-L-alaninyl) phosphorochloridate **6b** (3.7 ml of 0.197 g/ml solution, 2.1 mmol) and dry THF (10 ml). TLC (8 % MeOH in $CHCl_3$) showed the reaction to be complete after 3 hrs. The crude residue was purified by column chromatography, using MeOH:$CHCl_3$ (4:96) as eluent, to give the product as a clear, colourless oil, which solidified to a white foam after trituration and coevaporation with diethyl ether (0.314 g, 0.5 mmol, 75 %).
δ_P ($CDCl_3$, 121 MHz) 3.86, 3.87; δ_H ($CDCl_3$, 300 MHz) 0.65 (m, 2H, CH_2-cPr), 0.89 [m, 8H, CH_2-cPr and $(CH_2)_3$-cPent], 1.24 (m, 2H, CH_2-cPent), 1.41 (m, 3H, CH_3-ala), 1.65 (m, 2H, CH-cPent and 6'H_a), 2.81 (m, 1H, 6'H_b), 3.04 (m, 1H, CH-cPr), 3.19 (m, 1H, 4'**H**), 3.80 (m, 1H, CH-ala), 4.07 (m, 3H, OCH_2 and NH-ala), 4.22 (m, 2H, 5'**H**), 4.92 (bs, 2H, NH_2), 5.55 (m, 1H, 1'**H**), 5.81 (bs, 1H, NH-cPr), 5.92 (m, 1H, 3'**H**), 6.11 (m, 1H, 2'**H**), 7.26 (m, 5H, Ar**H**), 7.52 (d, 1H, 8H); δ_C ($CDCl_3$, 75 MHz) 6.42 (CH_2-cPr), 21.43 (CH_3-ala), 22.73 (CH-cPr), 24.59 (CH_2-cPcnt), 25.35 (CH_2-cPent), 26.64 (CH-cPent), 33.43, 33.51 (6'**C**), 44.58, 44.68 (4'**C**), 49.23 (CH-ala), 57.86, 57.91 (1'**C**), 64.69, 64.97 (O-CH_2-), 67.84 (5'**C**), 113.74 (5**C**), 119.09-119.18 (*p*-Ph), 123.88 (*o*-Ph), 128.62 (*m*-Ph), 130.05, 130.11 (3'**C**), 134.65, 134.76 (8**C**), 135.33, 135.44 (2'**C**), 149.63, 149.72 (6**C** and *ipso*-Ph), 154.98 (4**C**), 158.59 (2**C**), 172.50, 172.60 (C=O); *m/z* (FAB) 598.2745 (MH^+, $C_{29}H_{39}N_7O_5P$ requires 596.2750).

L-Alanine (cyclobutyl) ester p-toluene sulfonate salt

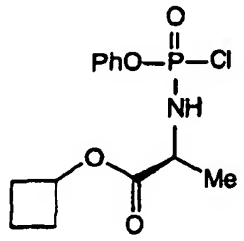
[0170]



[0171] Prepared according to **Standard Procedure 2**, except using benzene as solvent: from L-alanine (1.0 g, 11 mmol), *p*-TSA monohydrate (2.35 g, 12 mmol), cyclobutanol (0.9 ml, 11 mmol) and benzene (65 ml). The *p*-toluene sulfonate salt was isolated as a white solid (1.73 g, 5.5 mmol, 49 %).
δ_H (d_4-CH_3OH, 300 MHz) 1.51 (d, 3H, CH_3-ala, J= 7), 1.75 (m, 2H, CH_2-cBu), 2.14 (m, 2H, CH_2-cBu), 2.37 (m, 5H, CH_2-cBu and CH_3, *p*-TSA), 4.05 (q, 1H, CH-ala, J= 7), 5.08 (m, 1H, CH-cBu), 7.24 (d, 2H, Ar**H**, *p*-TSA), 7.70 (d, 2H, Ar**H**, *p*-TSA); δ_C (d_4-CH_3OH, 75 MHz) 14.57 (CH_2-cBu), 16.58 (CH_3-ala), 21.73 (CH_3-*p*TSA), 31.38, 31.44 (CH_2-cBu), 50.16 (CH-ala), 72.47 (CH-cBu), 127.35 (*o*-Ph, *p*-TSA), 130.23 (*m*-Ph, *p*-TSA), 142.13 (*ipso*-C-CH_3, *p*-TSA), 143.89 (*ipso*-C-S, *p*-TSA), 170.71 (C=O).

Phenyl(cyclobutoxy-L-alaninyl)phosphorochloridate

[0172]

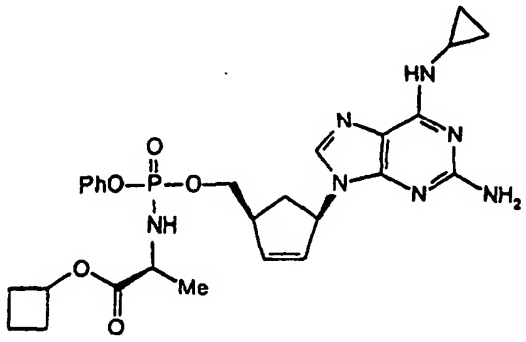


[0173] Prepared according to **Standard Procedure 3,** from phenyl dichlorophosphate (0.75 ml, 5.0 mmol), dry triethylamine (1.4 ml, 10.0 mmol), L-alanine (cyclopentane methyl) ester *p*-toluene sulfonate salt **7a** (1.58 g, 5.0 mmol) and dry DCM (65 ml total). The crude product was obtained as a clear, colourless oil (1.13 g, 71 %).
δ_P ($CDCl_3$, 121 MHz) 8.96, 9.33

[0174] The product was redissolved in dry THF (5 ml) and used as a 0.226 g/ml solution.

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl(cyclobutoxy-L-alaninyl)]phosphate [Cf 1775]

[0175]

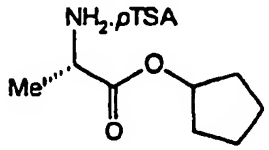


[0176] Prepared according to **Standard Procedure** 4, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), ^{t}BuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol) phenyl(cyclobutyl meth-oxy-L-alaninyl) phosphorochloridate **7b** (2.95 ml of 0.226 g/ml solution, 2.1 mmol) and dry THF (8 ml). TLC (8 % MeOH in $CHCl_3$) showed the reaction to be complete after 3.5 hrs. The crude residue was purified by column chromatography, using MeOH:$CHCl_3$ (4:96) as eluent, to give the product as a pale, yellow oil, which solidified to a cream solid after trituration and coevaporation with diethyl ether (0.238 g, 0.4 mmol, 60 %).
δ_P ($CDCl_3$, 121 MHz) 3.89, 3.93; δ_H ($CDCl_3$, 300 MHz) 0.63 (m, 2H, CH_2-cPr), 0.87 (m, 2H, CH_2-cPr), 1.39 (m, 3H, CH_3-ala), 1.65 (m, 2H, CH_2-cBu), 1.81 (m, 1H, 6'H_a), 2.04 (m, 2H, CH_2-cBu), 2.36 (m, 2H, CH_2-cBu), 2.80 (m, 1H, 6'H_b), 3.03 (m, 1H, **CH**-cPr), 3.17 (m, 1H, 4'**H**), 3.97 (m, 2H, NH-ala and CH-ala), 4.18 (m, 2H, 5'**H**), 4.98 (m, 3H, MH_2 and OCH), 5.55 (m, 1H, 1'**H**), 5.91 (m, 1H, 3'**H**), 6.01 (m, 1H, **NH**-cPr), 6.10 (m, 1H, 2'**H**), 7.25 (m, 5H, Ar**H**), 7.51 (d, 1H, 8**H**); δ_C ($CDCl_3$, 75 MHz) 7.80 (CH_2-cPr), 13.82 (CH_2-cBu), 21.42 (CH_3-ala), 22.06 (**CH**-cPr), 30.52-30.63 (CH_2-cBu), 35.01 (6'**C**), 46.01, 46.12 (4'**C**), 50.50 (CH-ala), 59.26 (1'**C**), 69.30 (**CH**-cBu), 70.19 (5'**C**), 115.25 (5**C**), 120.53, 120.59 (*p*-Ph), 125.28 (*o*-Ph), 130.05 (*m*-Ph), 131.53 (3'**C**), 135.97 (8**C**), 136.73, 136.85 (2'**C**), 151.08-151.17 (6**C** and

ipso-Ph), 156.71 (4C), 160.44 (2C), 173.33 (C=O).

L-Alanine (cyclopentyl) ester p-toluene sulfonate salt

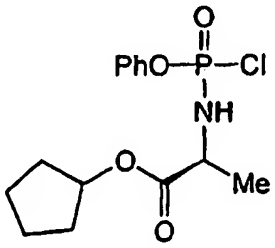
[0177]



[0178] Prepared according to **Standard Procedure 2**, except using benzene as solvent: from L-alanine (1.6 g, 18 mmol), *p*-TSA monohydrate (3.8 g, 20 mmol), cyclopentanol (1.6 ml, 18 mmol) and benzene (100 ml). The *p*-toluene sulfonate salt was isolated as a beige solid (2.81 g, 8.5 mmol, 47 %).
δ_H (d_4-CH_3OH, 300 MHz) 1.51 (d, 3H, CH_3-ala, J= 7), 1.71 (m, 6H, CH_2-cPnt), 1.92 (m, 2H, CH_2-cPnt), 2.39 (m, 5H, CH_2-cBu and CH_3, *p*-TSA), 4.04 (q, 1H, CH-ala, J = 7), 5.28 (m, 1H, CH-cPnt), 7.26 (d, 2H, ArH, *p*-TSA), 7.73 (d, 2H, ArH, *p*-TSA); δ_C (d_4-CH_3OH, 75 MHz) 16.59 (CH_3-ala), 21.72 (CH_3-*p*TSA), 24.97 (CH_2-cPnt), 33.81, 33.97 (CH_2-cPnt), 50.31 (CH-ala), 81.37 (CH-cPnt), 127.36 (*o*-Ph, *p*-TSA), 130.25 (*m*-Ph, *p*-TSA), 142.20 (*ipso*-C-CH_3, *p-TSA*), 143.79 (*ipso*-C-S, *p*-TSA), 171.17 (C=O).

Phenyl(cyclopentyloxy-L-alaninyl)phosphorochloridate

[0179]

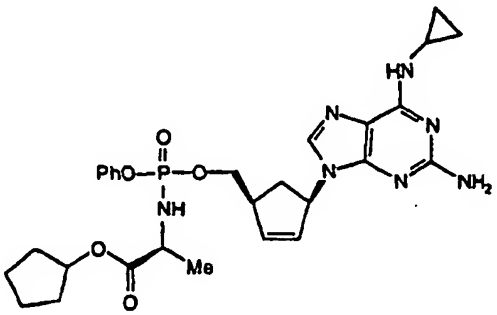


[0180] Prepared according to **Standard Procedure 3**, from phenyl dichlorophosphate (0.9 ml, 6.0 mmol), dry triethylamine (1.7 ml, 12.0 mmol), L-alanine (cyclopentane methyl) ester *p*-toluene sulfonate salt **8a** (1.98 g, 6.0 mmol) and dry DCM (100 ml total). The crude product was obtained as a clear, colourless oil (1.8 g, 91 %).
δ_P ($CDCl_3$, 121 MHz) 9.01, 9.37

[0181] The product was redissolved in dry THF (5 ml) and used as a 0.361 g/ml solution.

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl(cyclopentoxy-L-alaninyl)]phosphate [Cf 1776]

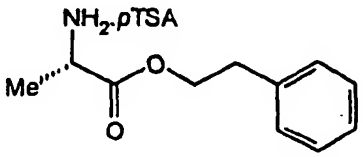
[0182]



[0183] Prepared according to **Standard Procedure 4**, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), ^{t}BuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol) phenyl(cyclobutyl meth-oxy-L-alaninyl) phosphorochloridate **8b** (1.93 ml of 0.361 g/ml solution, 2.1 mmol) and dry THF (8 ml). TLC (8 % MeOH in $CHCl_3$) showed the reaction to be complete after 3.5 hrs. The crude residue was purified twice by column chromatography, using MeOH:$CHCl_3$ (4:96) as eluent, to give the product as a clear, colourless oil, which solidified to a white foam after trituration and coevaporation with diethyl ether (0.254 g, 0.4 mmol, 62 %).
δ_P ($CDCl_3$, 121 MHz) 3.97, 3.98; δ_H ($CDCl_3$, 300 MHz) 0.64 (m, 2H, CH_2-cPr), 0.87 (m, 2H, CH_2-cPr), 1.38 (m, 3H, CH_3-ala), 1.67 (m, 7H, 3 × CH_2-cPent and 6'H_a), 1.86 (m, 2H, CH_2-cPent), 2.81 (m, 1H, 6'H_b), 3.04 (m, 1H, CH-cPr), 3.18 (m, 1H, 4'H), 3.96 (m, 2H, NH-ala and CH-ala), 4.21 (m, 2H, 5'H), 5.02 (bs, 1H, NH_2), 5.18 (m, 1H, OCH), 5.56 (m, 1H, 1'H), 5.91 (m, 1H, 3'H), 5.98 (bs, 1H, NH-cPr), 6.11 (m, 1H, 2'H), 7.25 (m, 5H, ArH), 7.51 (d, 1H, 8H); δ_C ($CDCl_3$, 75 MHz) 7.78 (CH_2-cPr), 21.42, 21.48 (CH_3-ala), 24.07 (CH-cPr), 32.91- (CH_2-cPent), 33.05, 33.08 (6'C), 34.97, 35.02 (CH_2-cPent), 46.02, 46.12 (4'C), 50.71 (CH-ala), 59.21, 59.25 (1'C), 69.22, 69.29 (5'C), 78.90 (OCH), 115.23 (5C), 120.55- 120.61 (*p*-Ph), 125.28 (*o*-Ph), 130.05 (*m*-Ph), 131.53, 131.59 (3'C), 135.87, 135.97 (8C), 136.73, 136.86 (2'C), 151.09, 151.18 (6C and *ipso*-Ph), 156.71 (4C), 160.44 (2C), 173.71, 173.80(C=O).

L-Alanine (phenethyl) ester p-toluene sulfonate salt

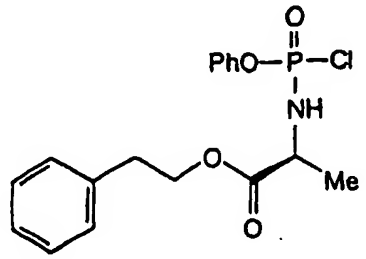
[0184]



[0185] Prepared according to **Standard Procedure 2**, from L-alanine (1.0 g, 11 mmol), *p*-TSA monohydrate (2.35 g, 12 mmol), phenethyl alcohol (1.3 ml, 11 mmol) and toluene (65 ml). The *p*-toluene sulfonate salt was isolated as an off-white solid (4.0 g, 10.9 mmol, 97 %). δ_H (d_4-CH_3OH, 300 MHz) 1.46 (d, 3H, CH_3-ala, *J*= 7), 2.32 (2, 3H, CH_3, *p*-TSA), 2.93 (t, 2H, CH_2Ph, *J*= 7), 4.07 (q, 1H, CH-ala, *J* = 7), 4.37 (m, 2H, O-CH_2) 7.22 (m, 7H, ArH, *p*-TSA and PhH), 7.78 (d, 2H, ArH, *p*-TSA); δ_C (d_4-CH_3OH, 75 MHz) 16.80 (CH_3-ala), 22.06 (CH_3-*p*TSA), 36.20 (CH_2-Ph), 50.41 (CH-ala), 68.28 (O-CH_2), 127.70, 127.83 (*o*-Ar and *o*-Ph, *p*-TSA), 129.81 (*p*-Ar), 130.13, 130.48 (*m*-Ar and *m*-Ph, *p*-TSA), 139.23 (*ipso*-ArC), 142.30 (*ipso*-C-CH_3, *p*-TSA), 143.83 (*ipso*-C-S, *p*-TSA), 171.44 (C=O).

Phenyl(phenethoxy-L-alaninyl)phosphorochloridate

[0186]

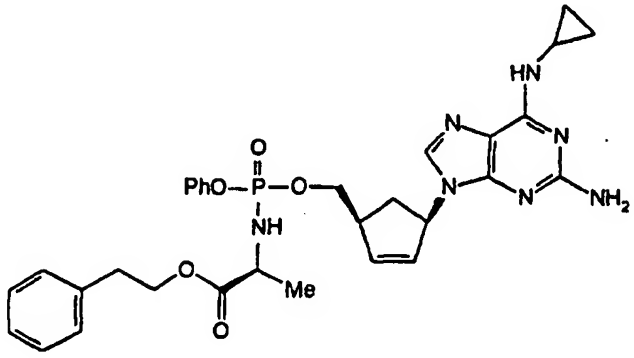


[0187] Prepared according to **Standard Procedure 3**, from phenyl dichlorophosphate (0.5 ml, 33 mmol), dry triethylamine (0.93 ml, 6.7 mmol), L-alanine (phenethyl) ester *p*-toluene sulfonate salt **9a** (1.232g, 3.3 mmol) and dry DCM (60 ml total). The crude product was obtained as a clear, colourless oil (1.16 g, 94 %).
δ_P ($CDCl_3$, 121 MHz) 8.93, 9.25

[0188] The product was redissolved in dry THF (5 ml) and used as a 0.233 g/ml solution.

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl(phenethoxy-L-alaninyl)]phosphate [Cf 1777]

[0189]

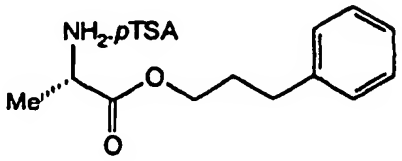


[0190] Prepared according to **Standard Procedure** 4, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), ^{t}BuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol) phenyl(phenethoxy-L-alaninyl) phosphor-ochloridate **9b** (3.3 ml of 0.233 g/ml solution, 2.1 mmol) and dry THF (8 ml). TLC (8 % MeOH in $CHCl_3$) showed the reaction to be complete after 3 hrs. The crude residue was purified twice by column chromatography, using MeOH:$CHCl_3$ (4:96) as eluent, to give the product as a pale, yellow oil, which solidified to a cream solid after trituration and coevaporation with diethyl ether (0.181 g, 0.3 mmol, 42 %).
δ_P ($CDCl_3$, 121 MHz) 3.81, 3.86; δ_H ($CDCl_3$, 300 MHz) 0.65 (m, 2H, CH_2-cPr), 0.89 (m, 2H, CH_2-cPr), 1.35 (m, 3H, CH_3-ala), 1.71 (m, 1H, 6'H_a), 2.80 (m, 1H, 6'H_b), 2.96 (m, 2H, CH_2Ph), 3.03 (m, 1H, CH-cPr), 3.17 (m, 1H, 4'H), 3.91 (m, 2H, NH-ala and CH-ala), 4.18 (m, 2H, OCH), 4.36 (m, 2H, 5'H), 4.99 (bs, 1H, NH_2), 5.56 (m, 1H, 1'H), 5.92 (m, 2H, 3'H and NH-cPr), 6.09 (m, 1H, 2'H), 7.26 (m, 10H, ArH and PhH), 7.52 (d, 1H, 8H); δ_C ($CDCl_3$, 75 MHz) 6.36 (CH_2-cPr), 19.98, 20.04 (CH_3-ala), 22.65 (CH-cPr), 33.46, 33.54 (6'C), 33.90 (CH_2-Ph), 44.56, 44.66 (4'C), 49.21 (CH-ala), 57.79, 57.85 (1'C), 64.84 (OCH_2), 67,82 (5'C), 113.79 (5C), 119.11-119.17 (*p*-Ph), 123.87 (*p*-Ar), 125.68 (*o*-Ph), 127.53 (*o*-Ar), 127.83 (*m*-Ph), 128.62 (*m*-Ar), 130.07, 130.14 (3'C), 134.48 (8C), 135.30, 135.39 (2'C), 136.25 (*ipso*-Ar),

149.63, 149.71 (6C and *ipso*-Ph), 155.25 (4C), 158.94 (2C), 172.75, 172.45 (C=O).

L-Alanine (3-phenyl-1-propyl) ester p-toluene sulfonate salt

[0191]



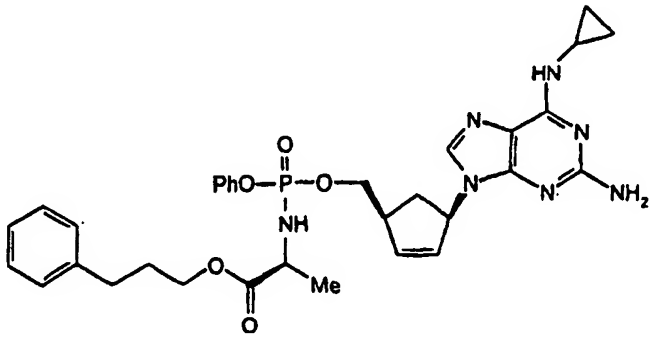
[0192] Prepared according to **Standard Procedure 2,** from L-alanine (1.0 g, 11 mmol), *p*-TSA monohydrate (2.35 g, 12 mmol), 3-phenyl-1-propanol (1.5 ml, 11 mmol) and toluene (65 ml). Removal of the solvent gave the crude product as a yellow oil. Diethyl ether was added and the mixture was cooled for 30 mins. The resulting suspension was filtered to give the *p*-toluene sulfonate salt as a white solid (4.24 g, 11.2 mmol, 100 %).
δ_H (d_4-CH_3OH, 300 MHz) 1.53 (d, 3H, CH_3-ala, J= 7), 1.97 (m, 2H, CH_2CH_2Ph), 2.34 (2, 3H, CH_3, *p*-TSA), 2.67 (t, 2H, CH_2Ph, J = 7), 4.10 (q, 1H, CH-ala, J = 7), 4.20 (t, 2H, O-CH_2, J = 7) 7.22 (m, 7H, ArH, *p*-TSA and PhH), 7.75 (d, 2H, ArH, *p*-TSA); δ_C (d_4-CH_3OH, 75 MHz) 16.77 (CH_3-ala), 21.93 (CH_3-*p*TSA), 31.63 (CH_2CH_2-Ph), 33.37 (CH_2-Ph), 50.44 (CH-ala), 67.27 (O-CH_2), 127.26-127.58 (*o*-Ar and *o*-Ph, *p*-TSA), 129.66-130.00 (*p*-Ar), 130.41 (*m*-Ar and *m*-Ph, *p*-TSA), 142.31 (*ipso*-ArC), 142.82 (*ipso*-C-CH_3, *p*-TSA), 143.82 (*ipso*-C-S, *p*-TSA), 171.47 (C=O).

Phenyl(phenethoxy-L-alaninyl)phosphorochloridate

[0193] Prepared according **to Standard Procedure 3,** from phenyl dichlorophosphate (0.5 ml, 3.3 mmol), dry triethylamine (0.93 ml, 6.7 mmol), L-alanine (3-phenyl-1-propyl) ester *p*-toluene sulfonate salt **9a** (1.27g, 3.3 mmol) and dry DCM (60 ml total). The crude product was obtained as a clear, pale brown oil (1.16 g, 90 %).
δ_P ($CDCl_3$, 121 MHz) 8.94, 9.27
The product was redissolved in dry THF (5 ml) and used as a 0.231 g/ml solution.

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl(3-phenyl-1-propoxy-L-alaninyl)]phosphate [Cf 1778]

[0194]

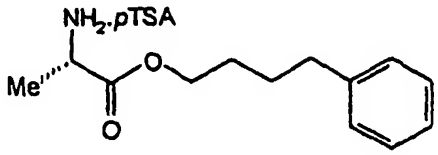


[0195] Prepared according to **Standard Procedure 4,** from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), ^{t}BuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol) phenyl(3-phenyl-1-propoxy-L-alaninyl) phosphorochloridate **10b** (3.5 ml of 0.231 g/ml solution, 2.1 mmol) and dry THF (8 ml).
[0196] TLC (8 % MeOH in $CHCl_3$) showed the reaction to be complete after 4 hrs. The crude residue was purified

three times by column chromatography, using MeOH:$CHCl_3$ (4:96) as eluent, to give the product as a pale, yellow oil, which solidified to an off-white foam after trituration and coevaporation with diethyl ether (0.330 g, 0.5 mmol, 75 %). δ_P ($CDCl_3$, 121 MHz) 3.89, 3.91; δ_H ($CDCl_3$, 300 MHz) 0.63 (m, 2H, CH_2-cPr), 0.88 (m, 2H, CH_2-cPr), 1.42 (m, 3H, CH_3-ala), 1.72 (m, 1H, 6'H_a), 1.98 (CH_2CH_2Ph), 2.69 (CH_2Ph), 2.80 (m, 1H, 6'H_b), 3.04 (m, 1H, CH-cPr), 3.18 (m, 1H, 4'H), 4.07 (m, 6H, NH-ala, CH-ala, OCH and 5'H), 5.00 (bs, 1H, NH_2), 5.56 (m, 1H, 1'H), 5.91 (m, 2H, 3'H and NH-cPr), 6.10 (m, 1H, 2'H), 7.25 (m, 10H, ArH and PhH), 7.52 (d, 1H, 8H); δ_C ($CDCl_3$, 75 MHz) 6.35 (CH_2-cPr), 20.06, 20.12 (CH_3-ala), 22.65 (CH-cPr), 29.02 (CH_2CH_2Ph), 30.97 (CH_2Ph), 33.48, 33.55 (6'C), 44.57, 44.67 (4'C), 49.26 (CH-ala), 57.78, 57.84 (1'C), 63.84 (OCH_2), 67.88 (5'C), 113.83 (5C), 119.10, 119.15 (*p*-Ph and *p*-Ar), 123.86 (*o*-Ph), 125.09 (*o*-Ar), 127.33, 127.47 (*m*-Ph), 128.63 (*m*-Ar), 130.10, 130.17 (3'C), 134.47, 134.58 (8C), 135.27, 135.37 (2'C), 139.81 (*ipso*-Ar), 149.65, 149.74 (6C and *ipso*-Ph), 155.27 (4C), 158.98 (2C), 172.49, 172.58 (C=O).

L-Alanine (4-phenyl-1-butyl) ester p-toluene sulfonate salt

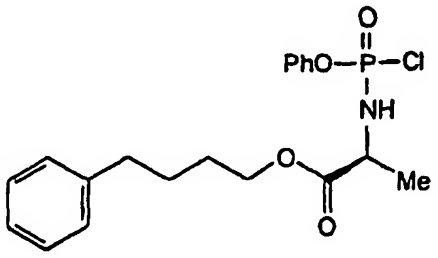
[0197]



[0198] Prepared according to **Standard Procedure 2,** from L-alanine (1.0 g, 11 mmol), *p*-TSA monohydrate (2.35 g, 12 mmol), 4-phenyl-1-butanol (1.7 ml, 11 mmol) and toluene (65 ml). Removal of the solvent gave the crude product as a clear, colourless oil, which solidified to a white solid after trituration and coevaporation with petrol (60/80) (4.4 g, 11.2 mmol, 100 %).
δ_H (d_4-CH_3OH, 300 MHz) 1.55 (d, 3H, CH_3-ala, J = 7), 1.74 (m, 4H, -$(CH_2)_2CH_2Ph$), 2.41 (2, 3H, CH_3, *p*-TSA), 2.67 (m, 2H, CH_2Ph), 4.12 (q, 1H, CH-ala, J = 7), 4.28 (m, 2H, O-CH_2) 7.25 (m, 7H, ArH, *p*-TSA and PhH), 7.75 (d, 2H, ArH, *p*-TSA); δ_C (d_4-CH_3OH, 75 MHz) 16.65 (CH_3-ala), 21.74 (CH_3-*p*TSA), 29.18, 29.50 ($OCH_2(CH_2)_2CH_2$-Ph), 36.72 (CH_2-Ph), 50.27 (CH-ala), 67.74 (O-CH_2), 127.31, 127.36 (*o*-Ar and *o*-Ph, *p*-TSA), 129.79 (*p*-Ar), 130.25 (*m*-Ar and *m*-Ph, *p*-TSA), 142.14 (*ipso*-ArC), 143.64, 143.87 (*ipso*-C-CH_3 and *ipso*-C-S, *p*-TSA), 171.47 (C=O).

Phenyl(4-phenyl-1-butoxy-L-alaninyl)phosphorochloridate

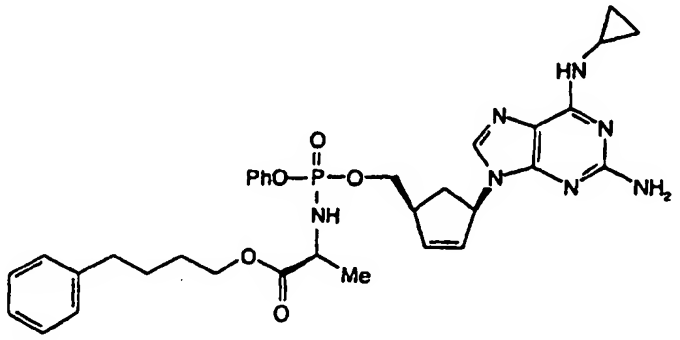
[0199]



[0200] Prepared according to **Standard Procedure 3,** from phenyl dichlorophosphate (0.5 ml, 3.3 mmol), dry triethylamine (0.93 ml, 6.7 mmol), L-alanine (4-phenyl-1-butyl) ester *p*-toluene sulfonate salt **11a** (1.32g, 3.3 mmol) and dry DCM (60 ml total). The crude product was obtained as a clear, pale brown oil (1.13 g, 85 %).
δ_P ($CDCl_3$, 121 MHz) 8.89, 9.24
[0201] The product was redissolved in dry THF (5 ml) and used as a 0.226 g/ml solution.

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl(4-phenyl-1-butoxy-L-alaninyl)]phosphate [Cf 1779]

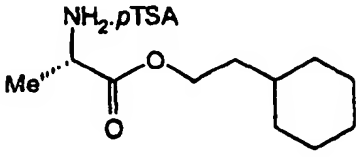
[0202]



[0203] Prepared according to **Standard Procedure 4**, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), ^{t}BuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol) phenyl(4-phenyl-1-butoxy-L-alaninyl) phosphorochloridate **11b** (3.7 ml of 0.226 g/ml solution, 2.1 mmol) and dry THF (8 ml). TLC (8 % MeOH in $CHCl_3$) showed the reaction to be complete after 4 hrs. The crude residue was purified by column chromatography, using MeOH:$CHCl_3$ (4:96) as eluent, to give the product as a clear, colourless oil, which solidified to an off-white foam after trituration and coevaporation with diethyl ether (0.314 g, 0.5 mmol, 69 %).
δ_P ($CDCl_3$, 121 MHz) 3.87, 3.90; δ_H ($CDCl_3$, 300 MHz) 0.65 (m, 2H, **CH**$_2$-cPr), 0.87 (m, 2H, **CH**$_2$-cPr), 1.41 (m, 3H, **CH**$_3$-ala), 1.71 (m, 5H, (**CH**$_2$)$_2$**CH**$_2$Ph and 6'**H**$_a$), 2.65 (m, 2H, **CH**$_2$Ph), 2.80 (m, 1H, 6'**H**$_b$), 3.04 (m, 1H, **CH**-cPr), 3.17 (m, 1H, 4'**H**), 4.06 (m, 6H, **NH**-ala, **CH**-ala, 5'**H** and O**CH**$_2$-) 5.02 (bs, 1H, **NH**$_2$), 5.56 (m, 1H, 1'**H**), 5.90 (m, 1H, 3'**H**), 5.98 (bs, 1H, NH-cPr), 6.10 (m, 1H, 2'**H**), 7.25 (m, 10H, Ar**H** and Ph**H**), 7.52 (d, 1H, 8**H**); δ_C ($CDCl_3$, 75 MHz) 6.35 (**C**H$_2$-cPr), 20.05. 20.11 (**C**H$_3$-ala), 22.65 (**C**H-cPr), 26.51 (CH$_2$**C**H$_2$CH$_2$Ph), 27.02 (**C**H$_2$(CH$_2$)$_2$Ph), 33.48, 33.55 (6'**C**), 34.32 (**C**H$_2$Ph), 44.56, 44.67 (4'**C**), 49.22, 49.26 (**C**H-ala), 57.79, 57.83 (1'**C**), 64.40 (O**C**H$_2$), 67.86, 67.94 (5'**C**), 113.75 (5**C**), 119.10, 119.15 (***p***-Ph and ***p***-Ar), 123.85 (***o***-Ph), 124.88 (***o***-Ar), 127.33, 127.35 (***m***-Ph), 128.61 (***m***-Ar), 130.07, 130.12 (3'**C**), 134.44, 134.54 (8**C**), 135.30, 135.39 (2'**C**), 140.76 (***Ipso***-Ar), 149.64-149.87 (6**C** and ***Ipso***-Ph), 155.26 (4**C**), 158.98 (2**C**), 172.53, 172.63 (C=O).

L-Alanine (2-cyclobexyl ethyl) ester p-toluene sulfonate salt

[0204]

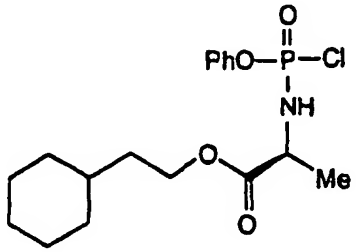


[0205] Prepared according to **Standard Procedure 2**, from L-alanine (1.0 g, 11 mmol), *p*-TSA monohydrate (2.35 g, 12 mmol), 2-cyclohexyl ethanol (1.56 ml, 11 mmol) and toluene (65 ml). Removal of the solvent gave the crude product as a clear, colourless oil, which solidified to a white solid after trituration and coevaporation with diethyl ether (2.8 g, 7.5 mmol, 67 %).
δ_H (d_4-CH_3OH, 300 MHz) 0.97 (m, 2H, **CH**$_2$), 1.24 (m, 4H, 2 × **CH**$_2$), 1.42 (m, 1H, CH-cHx), 1.54 (d, 3H, **CH**$_3$-ala, J = 7), 1.63 (m, 2H, **CH**$_2$), 1.75 (m, 4H, 2 × **CH**$_2$), 2.39 (s, 3H, **CH**$_3$, *p*-TSA), 4.09 (q, 1H, **CH**-ala, J = 7), 4.28 (m, 2H, O-**CH**$_2$), 7.25 (d, 2H, Ar**H**, *p*-TSA), 7.72 (d, 2H, Ar**H**, *p*-TSA); δ_C (d_4-CH_3OH, 75 MHz) 16.65 (**C**H$_3$-ala), 21.74 (**C**H$_3$-

*p*TSA), 27.68 (CH_2), 27.93 (CH_2), 34.58 (CH_2), 34.62 (CH_2), 36.10 (CH-cHx), 50.27 (CH-ala), 66.05 [O-$CH_2(CH_2)_2$], 127.36 (*o*-Ph, *p*-TSA), 130.24 (*m*-Ph, *p*-TSA), 142.13 (*Ipso*-C-CH_3, *p*-TSA), 143.89 (*Ipso*-C-S, *p*-TSA), 171.49 (C=O).

Phenyl(2-cyclohexyl ethoxy-L-alaninyl)phosphorochloridate

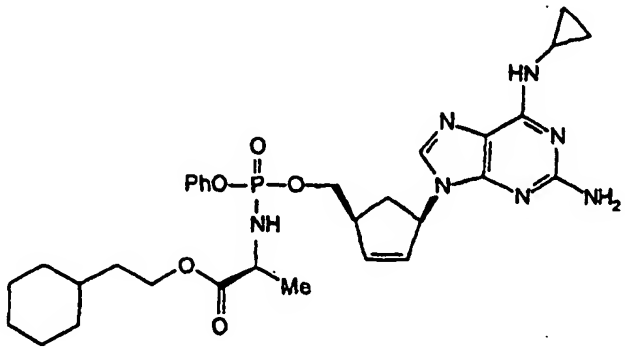
[0206]



[0207] Prepared according to **Standard Procedure 3**, from phenyl dichlorophosphate (0.9 ml, 6.0 mmol), dry triethylamine (1.7 ml, 12.0 mmol), L-alanine (cyclohexyl ethyl) ester *p*-toluene sulfonate salt **12a** (2.24g, 6.0 mmol) and dry DCM (100 ml total). The crude product was obtained as a clear, colourless oil (1.86 g, 83 %).
δ_P ($CDCl_3$, 121 MHz) 8.96, 9.31
The product was redissolved in dry THF (5 ml) and used as a 0.372 g/ml solution.

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl(2-cyclohexyl-1-ethoxy-L-alaninyl)]phosphate [Cf 1780]

[0208]

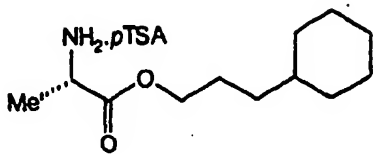


[0209] Prepared according to **Standard Procedure 4**, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclapentene-1-methanol (0.2 g, 0.7 mmol), ^{t}BuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol) phenyl(cyclohexyl ethoxy-L-alaninyl) phosphorochloridate **12b** (2.1 ml of 0.372 g/ml solution, 2.1 mmol) and dry THF (8 ml). TLC (8 % MeOH in $CHCl_3$) showed the reaction to be complete after 2.5 hrs. The crude residue was purified twice by column chromatography, using MeOH:$CHCl_3$ (4:96) as eluent, to give the product as a clear, colourless oil, which solidified to an off-white foam after trituration and coevaporation with diethyl ether (0.302 g, 0.5 mmol, 69 %).
δ_P ($CDCl_3$, 121 MHz) 3.91, 3.94; δ_H ($CDCl_3$, 300 MHz) 0.64 (m, 2H, CH_2-cPr), 0.91 (m, 4H, CH_2 and CH_2-cPr), 1.21 (m, 2H, CH_2), 1.41 (m, 3H, CH_3-ala), 1.52 (m, 2H, CH-cHx and 6'H_a), 1.70 (m, 6H, 3 × CH_2), 2.80 (m, 1H, 6'H_b), 3.04 (m, 1H, CH-cPr), 3.18 (m, 1H, 4'H), 4.10 (m, 6H, NH-ala, CH-ala, OCH_2 and 5'H), 5.03 (bs, 1H, NH_2), 5.56 (m, 1H, 1'H), 5.96 (m, 1H, 3'H), 5.98 (m, 1H, NH-cPr), 6.10 (m, 1H, 2'H), 7.25 (m, 5H, Ar), 7.51 (d, 1H, 8H); δ_C ($CDCl_3$, 75 MHz) 6.35 (CH_2-cPr), 20.05, 20.12 (CH_3-ala), 22.69 (CH-cPr), 25.11 (CH_2), 25.37 (CH_2), 32.04, 32.07 (6'C), 33.45, 33.58 (CH-cHx), 34.76 (CH_2), 44.58, 44.69 (4'C), 49.28 (CH-ala), 57.78, 57.83 (1'C), 62.88 (OCH_2), 67.86 (5'C), 113.82 (5C), 119.10-119.19 (*p*-Ph), 123.85 (*o*-Ph), 128.61 (*m*-Ph), 130.12 (3'C), 134.44, 134.54 (8C), 135.28, 135.38 (2'C),

149.66-149.94 (6C and *ipso*-Ph), 155.28 (4C), 155.99 (2C), 172.57, 172.66 (C=O).

L-Alanine (3-cyclohexyl-1-propyl) ester p-toluene sulfonate salt

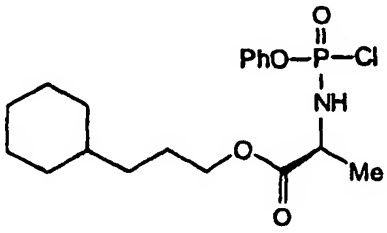
[0210]



[0211] Prepared according to **Standard Procedure 2**, from L-alanine (1.0 g, 11 mmol), *p*-TSA monohydrate (2.35 g, 12 mmol), 3-cyclohexyl-1-propanol (1.7 ml, 11 mmol) and toluene (65 ml). The solvent was removed and diethyl ether was added. The resulting suspension was filtered to give the product as a white solid (3.9 g, 10.1 mmol, 90 %). δ_H (d_4-CH_3OH, 300 MHz) 0.92 (m, 2H, CH_2), 1.23 (m, 6H, 3 × CH_2), 1.54 (d, 3H, CH_3-ala, J = 7), 1.71 (m, 7H, CH-cHx and 3 × CH_2), 2.39 (s, 3H, CH_3, *p*-TSA), 4.10 (q, 1H, CH-ala, J = 7), 4.22 (m, 2H, O-CH_2), 7.25 (d, 2H, ArH, *p*-TSA), 7.72 (d, 2H, ArH, *p*-TSA); δ_c (d_4-CH_3OH, 75 MHz) 16.66 (CH_3-ala), 21.74 (CH_3-*p*TSA), 27.36 (CH_2), 27.83 (CH_2), 28.11 (CH_2), 34.80 (CH_2), 34.90 (CH_2), 39.03 (CH-cHx), 50.27 (CH-ala), 68.27 (OCH_2), 127.36 (*o*-Ph, *p*-TSA), 130.24 (*m*-Ph, *p*-TSA), 142.12 (*ipso*-C-CH_3, *p*-TSA), 143.89 (*ipso*-C-S, *p*-TSA), 171.49 (C=O).

Phenyl(3-cyclohexyl-1-propoxy-L-alaninyl)phosphorochloridate

[0212]

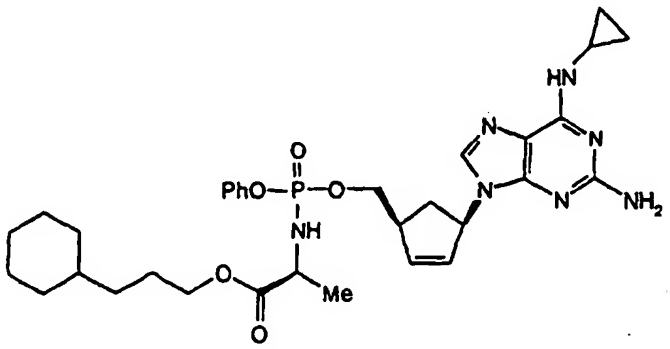


[0213] Prepared according to **Standard Procedure 3**, from phenyl dichlorophosphate (0.9 ml, 6.0 mmol), dry triethylamine (1.7 ml, 12.0 mmol), L-alanine (3-cyclohexyl-1-propyl) ester *p*-toluene sulfonate salt **13a** (2.32g, 6.0 mmol) and dry DCM (60 ml total). The crude product was obtained as a clear, pale yellow oil (2.31 g, 99 %).
δ_P ($CDCl_3$, 121 MHz) 8.99, 9.35

[0214] The product was redissolved in dry THF (5 ml) and used as a 0.463 g/ml solution.

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl(3-cyclohexyl-1-propoxy-L-alaninyl)]phosphate [Cf 1781]

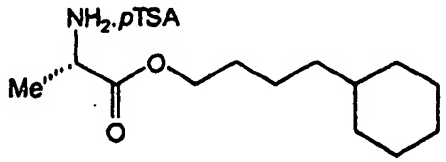
[0215]



[0216] Prepared according to **Standard Procedure 4**, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), ^{t}BuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol) phenyl(3-cyclohexyl-1-propoxy-L-alaninyl) phosphorochloridate **13b** (1.8 ml of 0.463 g/ml solution, 2.1 mmol) and dry THF (8 ml). TLC (8 % MeOH in $CHCl_3$) showed the reaction to be complete after 2.5 hrs. The crude residue was purified by column chromatography, using MeOH:$CHCl_3$ (4:96) as eluent, to give the product as a clear, colourless oil, which solidified to an off-white foam after trituration and coevaporation with diethyl ether (0.276 g, 0.4 mmol, 62 %).
δ_P ($CDCl_3$, 121 MHz) 3.89, 3.91; δ_H ($CDCl_3$, 300 MHz) 0.64 (m, 2**H**, CH_2-cPr), 0.89 (m, 2H, CH_2-cPr), 1.21 (m, 6H, 3 × CH_2), 1.41 (m, 3H, CH_3-ala), 1.66 (m, 8H, **CH**-cHx, 3 × CH_2 and 6'H_a), 2.81 (m, 1H, 6'H_b), 3.04 (m, 1H, **CH**-cPr), 3.18 (m, 1H, 4'**H**), 4.04 (m, 6H, **NH**-ala, **CH**-ala, OCH_2 and 5'**H**), 4.98 (bs, 1H, NH_2), 5.56 (m, 1H, 1'**H**), 5.91 (m, 1H, 3'**H** and NH-cPr), 6.11 (m, 1H, 2'**H**), 7.26 (m, 5H, Ar), 7.57 (d, 1H, 8**H**); δ_C ($CDCl_3$, 75 MHz) 6.37 (**C**H_2-cPr), 20.09, 20.15 (**C**H_3-ala), 22.66 (**C**H-cPr), 24.85 (**C**H_2), 25.27 (**C**H_2), 25.55 (**C**H_2), 29.92 (**C**H_2), 32.20, 32.33 (6'**C**), 33.49, 33.57 (**C**H-cHx), 36.22 (**C**H_2), 44.58, 44.68 (4'**C**), 49.27 (**C**H-ala), 57.78, 57.83 (1'**C**), 65.01 (O**C**H_2), 67.84 (5'**C**), 113.86 (5**C**), 119.10-119.19 (***p***-Ph), 123.85 (***o***-Ph), 128.61 (***m***-Ph), 130.12 (3'**C**), 134.47, 134.57 (8**C**), 135.28, 135.38 (2'**C**), 149.65-149.74 (6**C** and ***ipso***-Ph), 155.27 (4**C**), 158.96 (2**C**), 172.53, 172.64 (**C**=O).

L-Alanine (4-cyclohexyl-1-butyl) ester p-toluene sulfonate salt

[0217]

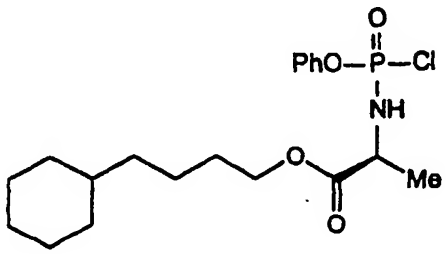


[0218] Prepared according to **Standard Procedure 2**, from L-alanine (0.51 g, 5.8 mmol), *p*-TSA monohydrate (1.21 g, 6.3 mmol), 4-cyclohexyl-1-butanol (1.0 ml, 5.8 mmol) and toluene (65 ml). The *p*-toluene sulfonate salt was obtained as a white crystalline solid (2.15 g, 5.4 mmol, 93 %).
δ_H (d_4-CH_3OH, 300 MHz) 0.92 (m, 2H, CH_2), 1.17 (m, 6H, 3 × CH_2), 1.39 (m, 2H, CH_2), 1.54 (d, 3H, CH_3-ala, J = 7), 1.69 (m, 7H, **CH**-cHx and 3 × CH_2), 2.39 (s, 3H, CH_3, *p*-TSA), 4.10 (q, 1H, **CH**-ala, J= 7), 4.24 (m, 2H, O-CH_2), 7.25 (d, 2H, ArH, *p*-TSA), 7.72 (d, 2H, ArH, *p*-TSA); δ_C (d_4-CH_3OH, 75 MHz) 16.66 (CH_3-ala), 21.74 (CH_3-*p*TSA), 24.51 (CH_2), 27.89 (CH_2), 28.18 (CH_2), 30.25 (CH_2), 34.90 (CH_2), 38.59 (CH_2), 39.27 (**C**H-cHx), 50.27 (**C**H-ala), 67.94 (OCH_2), 127.36 (***o***-Ph, *p*-TSA), 130.23 (***m***-Ph, *p*-TSA), 142.15 (***ipso***-**C**-CH_3, *p*-TSA), 143.89 (***ipso***-**C**-

S, *p*-TSA), 171.49 (C=O).

Phenyl(4-cyclohexyl-1-butoxy-L-alaninyl)phosphorochloridate

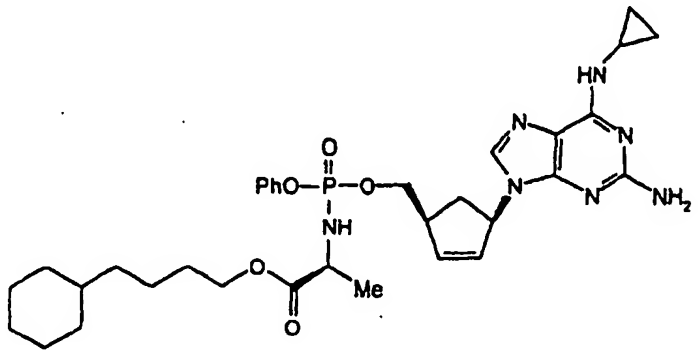
[0219]



[0220] Prepared according to **Standard Procedure 3**, from phenyl dichlorophosphate (0.45 ml, 3.0 mmol), dry triethylamine (0.8 ml, 6.0 mmol), L-alanine (4-cyclohexyl-1-butyl) ester *p*-toluene sulfonate salt **14a** (1.2g, 3.0 mmol) and dry DCM (60 ml total). The crude product was obtained as a clear, brown oil (1.36 g, >100 %).
δ_P ($CDCl_3$, 121 MHz) 8.91, 9.28
The product was redissolved in dry THF (5 ml) and used as a 0.272 g/ml solution.

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl(4-cyclohexyl-1-butoxy-L-alaninyl)]phosphate [Cf 1782]

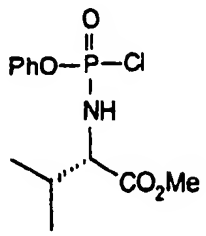
[0221]



[0222] Prepared according to **Standard Procedure** 4, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), ^{t}BuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol) phenyl(3-cycle-hexyl-1-propoxy-L-alaninyl) phosphorochloridate **14b** (3.1 ml of 0.272 g/ml solution, 2.1 mmol) and dry THF (8 ml). TLC (8 % MeOH in $CNCl_3$) showed the reaction to be complete after 2.5 hrs. The crude residue was purified twice by column chromatography, using MeOH:$CHCl_3$ (4:96) as eluent, to give the product as a clear, colourless oil, which solidified to an off-white foam after trituration and coevaporation with diethyl ether (0.341 g, 0.5 mmol, 75 %).
δ_P ($CDCl_3$, 121 MHz) 3.89, 3.91; δ_H ($CDCl_3$, 300 MHz) 0.65 (m, 2H, CH_2-cPr), 0.86 (m, 2H, CH_2-cPr), 1.21 (m, 8H, 4 × CH_2), 1.41 (m, 3H, CH_3-ala), 1.65 (m, 8H, CH-cHx, 3 × CH_2 and 6'H_a), 2.81 (m, 1H, 6'H_b), 3.04 (m, 1H, CH-cPr), 3.19 (m, 1H, 4'H), 4.04 (m, 6H, NH-ala, CH-ala, OCH_2 and 5'H), 4.96 (bs, 1H, NH_2), 5.56 (m, 1H, 1'H), 5.92 (m, 1H, 3'H and NH-cPr), 6.11 (m, 1H, 2'H), 7.26 (m, 5H, Ar), 7.52 (d, 1H, 8H); δ_C ($CDCl_3$, 75 MHz) 6.37 (CH_2-cPr), 20.10, 20.16 (CH_3-ala), 22.00 (CH_2), 22.65 (CH-cPr), 25.34 (CH_2), 25.64 (CH_2), 27.77 (CH_2), 32.28 (CH-cHx), 33.48, 33.56 (6'C), 36.45 (CH_2), 44.58, 44.68 (4'C), 49.24 (CH-ala), 57.79, 57.84 (1'C), 64.69 (OCH_2), 67.84, 67.94 (5'C), 113.86 (5C), 119.10-119.19 (*p*-Ph), 123.86 (*o*-Ph), 128.62 (*m*-Ph), 130.11, 130.17 (3'C), 134.47, 134.57 (8C), 135.28, 135.39 (2'C), 149.65-149.74 (6C and *ipso*-Ph), 155.26 (4C), 158.96 (2C), 172.54, 172.64 (C=O).

Phenyl(methoxy-L-valinyl)phosphorochloridate

[0223]

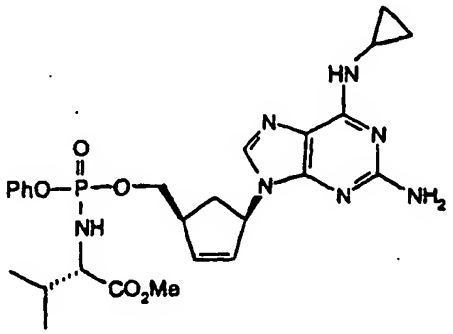


[0224] Prepared according to Standard Procedure 3, from phenyl dichlorophosphate (0.45 ml, 3.0 mmol), dry triethylamine (0.8 ml, 6.0 mmol), L-valine methyl ester hydrochloride salt (0.5 g, 3.0 mmol) and dry DCM (60 ml total). The crude product was obtained as a clear, colourless oil (0.922 g, >100 %).
δ_P ($CDCl_3$, 121 MHz) 8.99, 9.37

[0225] The product was redissolved in dry THF (5 ml) and used as a 0.184 g/ml solution.

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl(methoxy-L-valinyl)phosphate [Cf 1686]

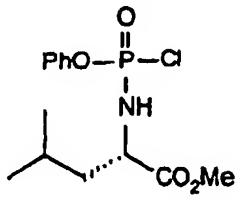
[0226]



[0227] Prepared according to **Standard Procedure 4**, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), ^{t}BuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol), phenyl(methoxy valinyl) phosphorochloridate **15a** (3.5 ml of 0.184 g/ml solution, 2.1 mmol) and dry THF (5 ml). The reaction mixture was stirred for 16 hrs, after which time a further 1.5 ml of the solution of **15a** was added. The reaction mixture was stirred for a further 4 hrs. The crude residue was purified by column chromatography, using MeOH:DCM (5:95) as eluent, to give the product as a clear, colourless oil, which solidified to a white foam after trituration and coevaporation with diethyl ether (0.161 g, 0.3 mmol, 41 %).
δ_P ($CDCl_3$, 121 MHz) 4.65, 4.74; δ_H ($CDCl_3$, 300 MHz) 0.66 (m, 2H, C**H**$_2$-cPr), 0.94 [m, 8H, C**H**$_2$-cPr and CH(C**H**$_3$)$_2$], 1.71 (m, 1H, 6'**H**$_a$), 2.06 [m, 1H, C**H**(CH$_3$)$_2$], 2.81 (m, 1H, 6'**H**$_b$), 3.04 (m, 1H, C**H**-cPr), 3.18 (m, 1H, **4'H**), 3.52 (m, 1H, C**H**-val), 3.70 (d, 3H, OC**H**$_3$), 3.83 (m, 1H, NH-val), 4.22 (m, 2H, 5'H), 4.86 (bs, 2H, N**H**$_2$), 5.56 (m, 1H, 1'**H**), 5.74 (bs, 1H, N**H**-cPr), 5.93 (m, 1H, 3'H), 6.11 (m, 1H, 2'H), 7.27 (m, 5H, Ar**H**), 7.52 (d, 1H, 8H); δ_C ($CDCl_3$, 75 MHz) 6.37 (**C**H$_2$-cPr), 16.36, 16.45 [CH(**C**H$_3$)$_2$], 22.65 (**C**H-cPr), 31.08, 31.16 [**C**H(CH$_3$)$_2$], 33.61 (6'**C**), 44.60, 44.70 (4'**C**), 51.05, 51.10 (O**C**H$_3$), 57.78 (1'**C**), 58.96, 59.01 (**C**H-val), 67.90 (5'**C**), 113.91 (5**C**), 119.03-119.13 (***o***-Ph), 123.80 (***p***-Ph), 128.58 (***m***-Ph), 130.05, 130.14 (3'**C**), 134.47 (8**C**), 135.27, 135.39 (2'**C**), 149.66-149.84 (6**C** and ***ipso***-Ph), 155.28 (4**C**), 158.96 (2**C**), 172.10, 172.19 (**C**=O); ***m/z*** (FAB) 556.2428 (MH^+, $C_{26}H_{35}N_7O_5P$ requires 556.2437).

Phenyl(metboxy-L-leucinyl)phosphorochloridate

[0228]

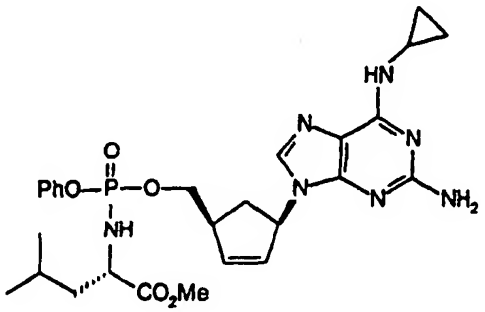


[0229] Prepared according to **Standard Procedure 3,** from phenyl dichlorophosphate (0.41 ml, 2.8 mmol), dry triethylamine (0.77 ml, 5.5 mmol), L-leucine methyl ester hydrochloride salt (0.5 g, 2.8 mmol) and dry DCM (60 ml total). The crude product was obtained as a clear, pale yellow oil (1.062 g, >100 %).
δ_P ($CDCl_3$, 121 MHz) 9.33, 9.51

[0230] The product was redissolved in dry THF (5 ml) and used as a 0.212 g/ml solution.

(1 S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl(methoxy-L-leucinyl)phosphate [Cf 1718]

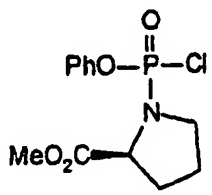
[0231]



[0232] Prepared according to **Standard Procedure 4**, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol 0.2 g, 0.7 mmol), ^tBuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol), phenyl (methoxy-L-leucinyl) phosphoro- chloridate **16a** (3.2 ml of 0.212 g/ml solution, 2.1 mmol) and dry THE (10 ml). TLC (8 % MeOH in $CHCl_3$) showed the reaction to be complete after 2 hrs. The crude residue was purified twice by column chromatography, using MeOH: $CHCl_3$ (4:96) as eluent, to give the product as a clear, colourless oil, which solidified to a white foam after trituration and coevaporation with diethyl ether (0.211 g, 0.4 mmol, 53 %).
δ_P ($CDCl_3$, 121 MHz) 3.98, 4.06; δ_H ($CDCl_3$, 300 MHz) 0.64 (m, 2H, CH_2-cPr), 0.89 [m, 8H, CH_2-cPr and $CH(CH_3)_2$], 1.51 (m, 2H, CH_2-leu), 1.69 [(m, 2H, $CH(CH_3)_2$ and 6'H_a], 2.80 (m, 1H, 6'H_b), 3.04 (m, 1H, CH-cPr), 3.16 (m, 1H, 4'H), 3.67 (m, 1H, CH-leu), 3.69 (d, 3H, OCH_3), 3.98 (m, 1H, NH-leu), 4.19 (m, 2H, 5'H), 4.97 (bs, 2H, NH_2), 5.55 (m, 1H, 1'H), 5.91 (m, 1H, NH-cPr and 3'H), 6.09 (m, 1H, 2'H), 7.25 (m, 5H, ArH), 7.51 (d, 1H, 8H); δ_C ($CDCl_3$, 75 MHz) 6.37 (CH_2-cPr), 20.69, 20.82 (CH_3-leu), 22.69 (CH-cPr), 23.28, 23.41 [$CH(CH_3)_2$], 33.54 (6'C), 42.60-42.81 (CH_2-leu), 44.59, 44.70 (4'C), 51.19, (OCH_3), 52.07, 52.16 (CH-leu), 57.80 (1'C), 67.91, 67.98 (5'C), 113.88 (5C), 118.99-119.14 (*o*-Ph), 123.80 (*p*-Ph), 128.58 (*m*-Ph), 130.06, 130.14 (3'C), 134.53 (8C), 135.27, 135.34 (2'C), 149.68-149.76 (6C and *ipso*-Ph), 155.28 (4C), 158.97 (2C), 173.12, 173.23 (C=O); ***m/z*** (FAB) 570.2610 (MH^+, $C_{27}H_{37}N_7O_5P$ requires 570.2594).

Phenyl(methoxy-L-prolinyl)phosphorochloridate

[0233]

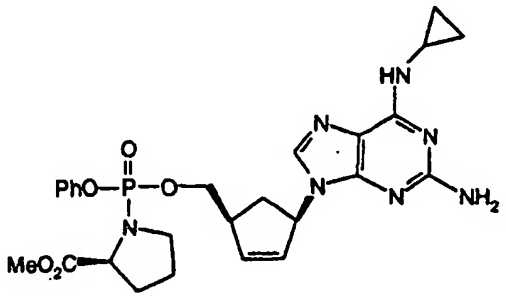


[0234] Prepared according to **Standard Procedure 3**, from phenyl dichlorophosphate (0.54 ml, 3.6 mmol), dry triethylamine (1.0 ml, 7.2 mmol), L-proline methyl ester hydrochloride salt (0.6 g, 3.6 mmol) and dry DCM (60 ml total). The crude product was obtained as a clear, colourless oil (1.24 g, >100 %).
δ_P ($CDCl_3$, 121 MHz) 9.02, 9.22

[0235] The product was redissolved in dry THF (5 ml) and used as a 0.248 g/ml solution.

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl(methoxy-L-prolinyl)phosphate [Cf 1719]

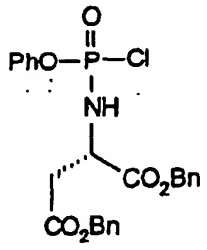
[0236]



[0237] Prepared according to **Standard Procedure 4**, from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.2 g, 0.7 mmol), ^{t}BuMgCl (1.0 M in THF: 1.4 ml, 1.4 mmol), phenyl(methoxy-L-prolinyl) phosphorochloridate 17a (2.6 ml of 0.248 g/ml solution, 2.1 mmol) and dry THE (10 ml). TLC (8 % MeOH in $CHCl_3$) showed the reaction to be complete after 20 hrs. The crude residue was purified twice by column chromatography, using MeOH: $CHCl_3$ (4:96) as eluent, to give the product as a clear, colourless oil, which solidified to a white foam after trituration and coevaporation with diethyl ether (0.168 g, 0.3 mmol, 44 %).
δ_P ($CDCl_3$, 121 MHz) 2.83, 2.90; δ_H ($CDCl_3$, 300 MHz) 0.65 (m, 2H, CH_2-cPr), 0.90 (m, 2H, CH_2-cPr), 1.92 (m, 5H, CH_2CH_2-pro and 6'H_a), 2.83 (m, 1H, 6'H_b), 3.04 (m, 1H, CH-cPr), 3.17 (m, 1H, 4'**H**), 3.45 (m, 2H, N-CH_2-pro), 3.70 (d, 3H, OCH_3), 4.13 (m, 1H, CH-pro), 4.30 (m, 2H, 5'**H**), 4.87 (bs, 2H, NH_2), 5.56 (m, 1H, 1'**H**), 5.73 (bs, 1H, NH-cPr), 5.91 (m, 1H, 3'**H**), 6.12 (m, 1H, 2'**H**), 7.27 (m, 5H, Ar**H**), 7.55 (d, 1H, 8**H**); δ_C ($CDCl_3$, 75 MHz) 6.42 (CH_2-cPr), 22.62 (CH-cPr), 23.91, 24.02 (CH_2-pro), 30.38, 30.49 (CH_2-pro), 33.54 (6'**C**), 44.61, 44.72 (4'**C**), 46.89 (N-CH_2), 51.07, 51.19 (OCH_3), 57.71, 57.80 (1'**C**), 58.84, 58.92 (CH-pro), 67.67, 67.75 (5'**C**), 113.87 (5**C**), 118.90-119.22 (*o*-Ph), 123.64, 123.73 (*p*-Ph), 128.55, 128.59 (*m*-Ph), 130.00 (3'**C**), 134.46 (8**C**), 135.42, 135.63 (2'**C**), 149.81, 149.90 (6**C** and *ipso*-Ph), 155.20 (4**C**), 158.87 (2**C**), 172.72, 173.23 (**C**=O); ***m/z*** (FAB) 554.2283 (MH^+, $C_{26}H_{33}N_7O_5P$ requires 554.2281).

Phenyl(dibenzyloxy-L-aspartinyl)phosphorochloridate

[0238]



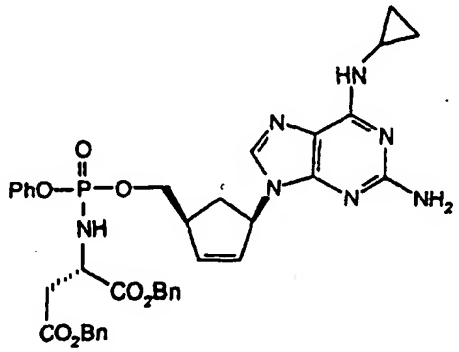
[0239] Prepared according to **Standard Procedure 3,** from phenyl dichlorophosphate (0.45 ml, 3.0 mmol), dry triethylamine (0.8 ml, 6.0 mmol), L-aspartate dibenzyl ester *p*-toluene sulfonate salt (1.46 g, 3.0 mmol) and dry DCM (60 ml total). The crude product was obtained as a clear, yellow oil (0.8024 g, 55 %).

δ_P ($CDCl_3$, 121 MHz) 9.43, 9.58

[0240] The product was redissolved in dry THF (5 ml) and used as a 0.16 g/ml solution.

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl(dibenzyloxy-L-aspartinyl)phosphate [Cf 1720]

[0241]



[0242] Prepared according to **Standard Procedure 4,** from (1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol (0.157 g, 0.55 mmol), ^{t}BuMgCl (1.0 M in THF: 1.1 ml, 1.1 mmol), phenyl(dibenzyloxy-1-aspartinyl) phosphorochloridate 18a (5.0 ml of 0.16 g/ml solution, 1.6 mmol) and dry THF (10 ml). TLC (8 % MeOH in $CHCl_3$) showed the reaction to be complete after 1.5 hrs. The crude residue was purifed twice by column chromatography, using MeOH: $CHCl_3$ (3:97) as eluent, to give the product as a clear, colourless oil, which solidified to an off-white foam after trituration and coevaporation with diethyl ether (0.284 g, 0.4 mmol, 70 %).

δ_P ($CDCl_3$, 121 MHz) 3.68, 4.24; δ_H ($CDCl_3$, 300 MHz) 0.63 (m, 2H, CH_2-cPr), 0.85 (m, 2H, CH_2-cPr), 1.63 (m, 1H, 6'H_a), 2.71 (m, 1H, 6'H_b), 3.06 (m, 2H, CH-cPr and 4'H), 4.14 (m, 2H, CH-asp, NH-asp), 4.34 (m, 2H, 5'H), 4.98 (bs, 2H, NH_2), 5.06 (d, 2H, OCH_2Ph). 5.13 (d, 2H, OCH_2Ph), 5.53 (m, 1H, 1'H), 5.88 (m, 2H, NH-cPr and 3'H), 6.01 (m, 1H, 2'H), 7.25 (m, 15H, ArH), 7.49 (d, 1H, 8H); δ_C ($CDCl_3$, 75 MHz) 6.35 (CH_2-cPr). 22.64 (CH-cPr), 33.40 (6'C), 37.44, 37.60 (CH_2-asp), 44.50, 44.57 (4'C), 50.20, 50.33 (CH-asp), 57.79 (1'C), 65.77 (OCH_2Ph), 66.65 (OCH_2Ph), 67.86, 68.00 (5'C), 113.85 (5C), 119.09-119.34 (*o*-Ph), 123.92 (*p*-Ph), 127.34-127.55 (*m*-Ph and *m/p*-Bn), 128.61 (*o*-Bn), 130.06 (3'C), 134.00 (*ipso*-Bn), 134.03 (*ipso*-Bn), 134.61 (8C), 135.23, 135.27 (2'C), 149.47-149.91 (6C and *ipso*-Ph), 155.28 (4C), 158.95 (2C), 169.22, 169.43, 170.00, 170.29 (C=O).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl (2-methylpropyl) oxy-L-alaninyl phosphate) CF1672

[0243] This was prepared by Standard Procedure 4. 70% yield.
δ_P 3.87, 3.91.
δ_H 0.64 (2H, m, CH_aH_b, $CH_{a'}H_{b'}$ cyclopropyl), 0.92 (8H, m, CH_aH_b, $CH_{a'}H_{b'}$ cyclopropyl, $CH(CH_3)_2$), 1.42 (3H, m, CH_3 alaninyl), 1.71 (1H, m, 6'-H_aH_b), 1.92 (1H, m, **CH**$(CH_3)_2$), 2.81 (1H, m, 6'-H_aH_b), 3.03 (1H, m, CH cyclopropyl), 3.19 (1H, m, 4'-H), 3.87 (3H, m, **CH** alaninyl, $\mathbf{CH_2}CH(CH_3)_2$), 4.09 (1H, m, NH alaninyl), 4.20 (2H, m, 5'-H), 4.91 (2H, br s, NH_2), 5.53 (1H, br m, 1'-H), 5.80 (1H, br s, NH-cyclopropyl), 5.92 (1H, m, 3'-H), 6.12 (1H, m, 2'-H), 7.31 (5H, m, Ph-H), 7.48 (1H, br d, 8H)
δ_C 5.45 (CH_2-cyclopropyl x 2), 17.01 (CH($\mathbf{CH_3}$)$_2$), 19.23, 19.29 (Me alaninyl), 21.74 (CH-cyclopropyl), 25.72 (**CH**$(CH_3)_2$), 32.58, 32.64 (6'-C), 43.66, 43.76 (4'-C), 48.35 (CH alaninyl), 56.90 (1'-C), 66.88, 66.96, 67.03 (5'-C). 69.57, 69.60 ($\mathbf{CH_2}CH(CH_3)_2$), 118.17, 118.20, 118.24, 118.27 (*o*-Ph, 5-C), 122.94 (*p*-Ph), 127.70 (*m*-Ph), 129.19, 129.24 (3'-C), 134.35, 134.45 (8-C, 2'-C), 148.81, 148.72 (*i*-Ph), 149.62, 149.76 (6-C), 154.34 (4-C), 158.91, 158.96 (2-C), 171.68, 171.58 (C(O) alaninyl).
MS m/e 570.2505 (M^+, $C_{27}H_{36}N_7O_5P$ requires 570.2515).
HPLC t_R 33.11 min (0% CH_3CN (0 min), 80% CH_3CN (35 min), 80% CH_3CN (45 min), 0% CH_3CN (55 min)).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl (2,2-dimethylpropyl)oxy-L-alaninyl phosphate) CF1673

[0244] This was prepared by Standard Procedure 4. 94% yield.
δ_P 3.88, 3.94.
δ_H 0.61 (2H, m, CH_aH_b, $CH_{a'}H_{b'}$ cyclopropyl), 0.85 (2H, br m, CH_aH_b, $CH_{a'}H_{b'}$ cyclopropyl), 0.91 (9H, s, C($\mathbf{CH_3}$)$_3$), 1.41 (3H, m, CH_3 alaninyl), 1.70 (1H, m, 6'-H_aH_b), 2.78 (1H, m, 6'-H_aH_b), 3.03 (1H, m, CH cyclopropyl), 3.18 (1H, m, 4'-H), 3.81 (3H, m, **CH** alaninyl, $\mathbf{CH_2}CH(CH_3)_2$), 4.09 (1H, m, NH alaninyl), 4.20 (2H, m, 5'-H), 4.97 (2H, br s, NH2), 5.52 (1H, br m, 1'-H), 5.86 (1H, br s, NH-cyclopropyl, 3'-H), 6.08 (1H, m, 2'-H), 7.25 (5H, m, Ph-H), 7.48 (1H, br d, 8H).
δ_C 7.89 (CH_2-cyclopropyl x 2), 21.74, 21.77 (Me alaninyl), 26.81 (C($\mathbf{CH_3}$)$_3$), 24.21 (CH-cyclopropyl), 31.90 (**C**$(CH_3)_3$), 35.06 (6'-C), 46.10, 46.20 (4'-C), 50.79, 50.83 (CH alaninyl), 59.42 (1'-C), 66.35 (5'-C), 69.34, 69.41, 69.49 ($\mathbf{CH_2}C(CH_3)_3$), 116.41 (5-C), 120.62, 120.66, 120.68, 120.72 (*o*-Ph), 125.39 (*p*-Ph), 130.15 (*m*-Ph), 131.61, 131.65 (3'-C), 136.82, 136.90 (8-C, 2'-C), 151.16, 151.25 (6-C, *i*-Ph), 156.78 (4-C), 158.91, 160.44 (2-C), 174.09, 174.20 (**C**(O) alaninyl).
ES+ m/e 584.2640 (MH^+, $C_{28}H_{39}N_7O_5P$ requires 584.2672).
HPLC t_R 34.97 min (0% CH_3CN (0 min), 80% CH_3CN (35 min), 80% CH_3CN (45 min), 0% CH_3CN (55 min)).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl (3-methylbutyl) oxy-L-alaninyl phosphate) CF1674

[0245] This was prepared by Standard Procedure 4.47% yield.
δ_P 3.87, 3.89:
δ_H 0.57 (2H, m, CH_aH_b, $CH_{a'}H_{b'}$ cyclopropyl), 0.80 (8H, m, CHaH_b, $CH_{a'}H_{b'}$ cyclopropyl, $CH(\mathbf{CH_3})_2$), 1.30 (3H, m, CH_3 alaninyl), 1.42 (2H, m. $OCH_2\mathbf{CH_2}$), 1.62 (2H, m, 6'-$\mathbf{H_aH_b}$, **CH**$(CH_3)_2$), 2.70 (1H, m, 6'-$H_a\mathbf{H_b}$), 2.92 (1H, br s, CH cyclopropy]), 3.07 (1H, m, 4'-H), 3.88 (3H, m, CH alaninyl, $\mathbf{OCH_2}CH_2$), 4.07 (3H, m, NH alaninyl, 5'-H), 4.91 (2H, br s, NH_2), 5.48 (1H, br m, 1'-H), 5.83 (2H, br s, NH-cyclopropyl, 3'-H), 6.03 (1H, m, 2'-H), 7.18 (5H, m, Ph-H), 7.42 (1H, br d, 8H).
δ_C 7.81 (CH_2-cyclopropyl x 2), 21.49, 21.56 (Me alaninyl), 22.79, 22.83 (CH($\mathbf{CH_3}$)$_2$), 24.10 (**CH**$(CH_3)_2$), 25.38 (CH-cyclopropyl), 34.91, 34.99 (OCH_2CH_2), 37.54 (6'-C), 46.01, 46.11 (4'-C), 50.70 (CH alaninyl), 59.25, 59.29 (1'-C), 64.63, 64.66 ($\mathbf{OCH_2}CH_2$), 69.22, 69.30, 69.38 (5'-C), 116.17 (5-C), 120.53, 120.55, 120.59, 120.61 (*o*-Ph), 125.28 (*p*-Ph), 130.05 (*m*-Ph), 131.54, 131.60 (3'-C), 135.96 (8-C), 136.70, 136.81 (2'-C), 151.09, 151.17 (6-C, *i*-Ph), 156.68 (4-C), 160.34 (2-C), 173.94, 174.05 (C(O) alaninyl).
ES+ m/e 584.2664 (MH^+, $C_{28}H_{39}N_7O_5P$ requires 584.2672).
HPLC t_R 38.51 min (0% CH_3CN (0 min), 80% CH_3CN (35 min), 80% CH_3CN (45 min), 0% CH_3CN (55 min)).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl (cycloheptanyl) oxy-L-alaninyl phosphate) CF1752

[0246] This was prepared by Standard Procedure 4.41% yield. δ_P 3.96, 3.98.
δ_H 0.68 (2H, m, CH_aH_b, $CH_{a'}H_{b'}$ cyclopropyl), 0.99 (2H, m, CH_aH_b, $CH_{a'}H_{b'}$ cyclopropyl), 1.36 (5H, m, CH_3 alaninyl, 5"-H_aH_b, 6"-H_aH_b), 1.80 (11H, m, 6'-H_aH_b, 2"-H, 3"-H, 4"-H, 7"-H, 5"-H_aH_b, 6"-H_aH_b), 2.80 (1H, m, 6'-H_aH_b), 3.12 (1H,

br s, CH cyclopropyl), 3.22 (1H, m, 4'-H), 3.97 (2H, m, CH alaninyl, NH alaninyl), 4.20 (2H, m, 5'-H), 4.95 (1H, m, O-CH), 5.18 (2H, br s, NH_2), 5.57 (1H, br m, 1'-H), 5.90 (1H, m, 3'-H), 6.12 (1H, m, 2'-H), 6.25 (1H, br s, NH cyclopropyl), 7.25 (5H, m, Ph-H), 7.51 (1H, br d, 8H).

δ_C 15.08 (CH_2-cyclopropyl x 2), 28.76, 28.82 (Me alaninyl), 30.40, 30.44 (3"-C, 6"-C), 24.10 ($CH(CH_3)_2$), 31.57 (CH-cyclopropyl), 35.87 (4"-C, 5"-C), 41.26, 41.29, 41.31, 41.36 (6'-C), 42.24 (2"-C, 7"-C), 53.32, 53.42 (4'-C), 58.08 (CH alaninyl), 61.15 (1'-C), 66.62 (5'-C), 116.17 (5-C), 127.81, 127.85, 127.88, 127.91 (o-Ph), 132.54 (*p*-Ph), 137.32, 137.49 (*m*-Ph), 138.75 (3'-C), 143.21 (8-C), 144.13, 144.22 (2'-C), 158.40, 158.49 (6-C, *i*-Ph), 164.42 (4-C), 167.41 (2-C), 180.47, 180.51, 180.59 (C(O) alaninyl).

ES+ m/e 632.2719 ($M[Na]^+$, $C_{30}H_{40}N_7O_5NaP$ requires 632.2726).

HPLC t_R 41.92 min (0% CH_3CN (0 min), 80% CH_3CN (35 min), 80% CH_3CN (45 min), 0% CH_3CN (55 min)).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl diethoxy-L-aspartyl phosphate) CF1714

[0247] This was prepared by Standard Procedure 4.54% yield.

δ_P 3.76, 4.19.

δ_H 0.62 (2H, m, CH_aH_b, $CH_{a'}H_{b'}$ cyclopropyl), 0.88 (2H, m, CH_aH_b, $CH_{a'}H_{b'}$ cyclopropyl), 1.25 (6H, m, $\mathbf{CH_3}$-CH_2-O aspartyl x 2), 1.68 (1H, m, 6'-H_aH_b). 2.75 (2H, m, -(CO)-$\mathbf{CH_aH_b}$ aspartyl, 6'-H_aH_b), 2.97 (2H, m, CH cyclopropyl, -(CO)-CH_aH_b aspartyl), 3.16 (1H, m, 4'-H), 4.15 (8H, m, CH aspartyl, CH_2-O aspartyl x 2, NH aspartyl, 5'-H), 4.90 (2H, br s, NH_2), 5.52 (1H, br m, 1'-H), 5.80 (1H, br s, NH-cyclopropyl), 5.90 (1H, m, 3'-H), 6.08 (1H, m, 2'-H), 7.21 (5H, m, Ph-H), 7.48 (1H, br d, 8H).

δ_C 8.65 (CH_2-cyclopropyl x 2), 15.31 ($\mathbf{CH_3}$-CH_2-O aspartyl x 2), 24.92 (CH-cyclopropyl), 35.72 ((CO)-$\mathbf{CH_2}$ aspartyl), 39.74, 39.91 (6'-C), 46.82, 46.90 (4'-C), 52.41, 52.47 (CH aspartyl), 60.11 (1'-C), 62.22 (CH_3-$\mathbf{CH_2}$-O(CO)CH_2 aspartyl), 63.15 (CH_3-$\mathbf{CH_2}$-O(CO)CH aspartyl), 70.14, 70.27, 70.35 (5'-C), 116.12 (5-C), 121.33, 121.40, 121.49, 121.55 (*o*-Ph), 126.15 (*p*-Ph), 130.86 (*m*-Ph), 132.36 (3'-C), 136.90 (8-C), 137.54 (2'-C), 151.81, 151.85 (6-C, *i*-Ph), 157.39 (4-C), 161.01 (2-C), 171.67, 171.81 ($\mathbf{C}$(O)CH_2 aspartyl), 172.38, 172.48, 172.52, 172.62 (C(O) aspartyl).

ES+ m/e 614.2393 (MH^+, $C_{28}H_{37}N_7O_7P$ requires 614.2492).

HPLC t_R 30.37 min (0% CH_3CN (0 min), 80% CH_3CN (35 min), 80% CH_3CN (45 min), 0% CH_3CN (55 min)).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl methoxy-L-methionyl phosphate) CF1715

[0248] This was prepared by Standard Procedure 4.49% yield.

δ_P 3.90, 4.03.

δ_H 0.61 (2H, m, CH_aH_b, $CH_{a'}H_{b'}$ cyclopropyl), 0.86 (2H, m, CH_aH_b, $CH_{a'}H_{b'}$ cyclopropyl), 1.71 (1H, m, CH-$\mathbf{CH_a}CH_b$ methioninyl), 1.90 (1H, m, CH-$CH_a\mathbf{CH_b}$ methioninyl), 2.01 (3H, d, CH3-S-), 2.30 (1H, m, 6'-H_aH_b), 2.47 (2H, m, 5'-CH_2), 2.78 (1H, m, 6'-H_aH_b), 2.97 (1H, br m, CH cyclopropyl), 3.14 (1H, m, 4'-H), 3.70 (3H, d, CH_3-O-), 3.80 (1H, m, CH methioninyl) 4.17 (3H, m, NH methioninyl, 5'-H), 4.89 (2H, br s, NH_2), 5.49 (1H, m, 1'-H), 5.80 (1H, br s, NH-cyclopropyl), 5.90 (1H, m, 3'-H), 6.08 (1H, m, 2'-H), 7.24 (5H, m, Ph-H), 7.43 (1H, br d, 8H).

δ_C 6.52 (CH_2-cyclopropyl x 2), 14.42, 14.47 (CH_3-S-), 22.81 (CH-cyclopropyl), 28.63, 28.78 (S-CH_2), 32.62, 32.73, 32.81 (CH-CH_2- methioninyl), 33.65 (6'-C), 44.73, 44.83 (4'-C), 51.67 (CH methioninyl), 57.99 (1'-C), 68.13, 68.20, 68.27 (5'-C), 114.03 (5-C), 119.15, 119.22, 119.24, 119.30 (*o*-Ph), 124.05, 124.10 (*p*-Ph), 128.80 (*m*-Ph), 130.26, 130.30 (3'-C), 134.72 (8-C), 135.42, 135.47 (2'-C), 149.76, 149.80, 149.84, 149.89 (*i*-Ph), 150.08 (6-C), 155.38 (4-C), 159.06 (2-C), 172.25, 172.28, 172.32, 172.36 ($\mathbf{C}$(O)).

ES+ m/e 588.2053 (MH^+, $C_{26}H_{34}N_7O_5PS$ requires 588.2080).

HPLC t_R 29.64 min (0% CH_3CN (0 min), 80% CH_3CN (35 min), 80% CH_3CN (45 min), 0% CH_3CN (55 min)).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl methoxy-L-tryptophanyl phosphate) CF1750

[0249] This was prepared by Standard Procedure 4. 70% yield.

δ_P 3.88, 4.01.

δ_H 0.68 (2H, m, CH_aH_b, $CH_{a'}H_{b'}$ cyclopropyl), 0.92 (2H, m, CH_aH_b, $CH_{a'}H_{b'}$ cyclopropyl), 1.53 (1H, m, 6'-H_aH_b), 2.68 (1H, m, 6'-H_aH_b), 2.99 (2H, br m, CH cyclopropyl, 4'-H), 3.22 (2H, m, CH_2-Trp), 3.66 (3H, d, CH_3-O-), 3.93 (3H, m, NH Trp, 5'-H), 4.35 (1H, m, CH Trp), 4.94 (2H, br s, NH_2), 5.49 (1H, m, 1'-H), 5.87 (2H, m, NH-cyclopropyl, 3'-H), 5.97 (1H, m, 2'-H), 7.01 (1H, m, 6"-H), 7.26 (7H, m, Ph-H, 4"-H, 5"-H), 7.46 (1H, m, 7"-H), 7.52 (1H, m, 2"-H), 8.63 (1H, br d, 8H).

δ_C 7.81 (CH_2-cyclopropyl x 2), 24.10 (CH-cyclopropyl), 34.86, 34.91 (6'-C), 45.81, 45.90, 46.00 (4'-C), 52.97 (CH Trp), 59.24, 59.29 (1'-C), 69.14, 69.20 (5'-C), 109.86, 110.11 (3"-C), 111.72 (7"-C), 118.91 (5-C), 119.95, 120.04 (4"-C, 5"-C),

120.40, 120.47, 120.57, 120.63 (*o*-Ph), 122.49, 122.56 (6"-H), 123.70 (2"-C), 125.23, 125.29 (*p*-Ph), 127.79, 127.98 (9"-C), 130.04 (*m*-Ph), 131.27 (3'-C), 136.08 (8-C), 136.50, 136.55, 136.76, 136.87 (2'-C, 8"-C), 151.05, 151.14, 151.17, 151.26 (*i*-Ph, 6-C), 156.68 (4-C), 160.35 (2-C), 173.58, 173.66 (**C**(O)).
ES+ m/e 643.2432 (MH^+, $C_{32}H_{36}N_8O_5P$ requires 643.2546).
HPLC t_R 31.46 min (0% CH_3CN (0 min), 80% CH_3CN (35 min), 80% CH_3CN (45 min), 0% CH_3CN (55 min)).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl methoxy-L-isoleucinyl phosphate) CF1751

[0250] This was prepared by Standard Procedure 4.60% yield.
δ_P 4.48, 4.54.
δ_H 0.68 (2H, m, CH_aH_b, CH_a,H_b, cyclopropyl), 0.91 (8H, m, CH_aH_b, CH_a,H_b,cyclopropyl, CH_3 x 2 isoleucinyl), 1.15 (1H, m, CH_aCH_b isoleucinyl), 1.45 (1H, m, CH_aCH_b isoleucinyl), 1.75 (2H, m, 6'-H_aH_b, CH_3**CH**), 2.83 (1H, m, 6'-H_aH_b), 3.05 (1H, br m, CH cyclopropyl), 3.19 (1H, m, 4'-H), 3.62 (1H, m, NH isoleucinyl), 3.71 (3H, d, CH_3-O-), 3.88 (1H, m, CH isoleucinyl), 4.21 (2H, m, 5'-H), 4.91 (2H, br s, NH_2), 5.55 (1H, m, 1'-H), 5.81 (1H, br s, NH-cyclopropyl), 5.93 (1H, m, 3'-H), 6.12 (1H, m, 2'-H), 7.28 (5H, m, Ph-H). 7.52 (1H, br d, 8H).
δ_C 7.82 (CH_2-cyclopropyl x 2), 11.89 (**CH_3**CH_2), 15.72 (**CH_3**CH), 24.08 (CH-cyclopropyl), 25.04, 25.13 (CH_3**CH_2**), 34.99 (6'-C), 39.49, 39.56, 39.64 (CH_2**CH**), 46.04, 46.14 (4'-C), *52.46*, 52.50 (CH isoleucinyl), 59.24, 59.44, 59.54 (1'-C), 69.34 (5'-C), 116.12 (5-C), 120.47, 120.53, 120.58 (*o*-Ph), 125.27 (*p*-Ph), 130.03 (*m*-Ph), 131.50, 131.57 (3'-C), 136.04 (8-C), 136.84, 136.74 (2'-C), 151.10, 151.18, 151.27 (*i*-Ph, 6-C), 156.69 (4-C), 161.06, 161.09, 161.35, 161.41 (2-C), 173.48, 173.53 (C(O)).
ES+ m/e 570.2496 (MH^+, $C_{27}H_{37}N_7O_5P$ requires 570.2594).
HPLC t_R 32.83, 33.14 min (0% CH_3CN (0 min), 80% CH_3CN (35 min), 80% CH_3CN (45 min), 0% CH_3CN (55 min)).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl dimethoxy-L-glutamyl phosphate) CF1749

[0251] This was prepared by Standard Procedure 4.38% yield.
δ_P 3.99.
δ_H 0.68 (2H, m, CH_aH_b, CH_a,H_b, cyclopropyl), 0.91 (2H, m, CH_aH_b, CH_a,H_b, cyclopropyl), 1.73 (1H, m, 6'-H_aH_b), 2.12 (1H, m, C(O)$CH_2CH_aH_b$), 2.38 (2H, m, C(O)CH_2), 2.82 (1H, m, 6'-H_aH_b), 3.05 (1H, m, CH cyclopropyl), 3.18 (1H, m, 4'-H), 3.68 (3H, s, MeOC(O)CH_2), 3.72 (3H, s, MeOC(O)CH), 3.85 (1H, m, NH glutyl), 4.10 (1H, m, CH glutyl), 4.21 (2H, m, 5'-H), 4.95 (2H, br s, NH_2), 5.57 (1H, br m, 1'-H), 5.88 (1H, br s, NH-cyclopropyl), 5.95 (1H, m, 3'-H), 6.10 (1H, m, 2'-H), 7.25 (5H, in, Ph-H), 7.54 (1H, br s, 8H).
δ_C 7.82 (CH_2-cyclopropyl x 2), 24.12 (CH-cyclopropyl), 29.66, 29.73, 29.88 (C(O)CH_2**CH_2**), C(O)**CH_2**CH_2), 34.91 (6'-C), 46.02, 46.12 (4'-C), 52.19 ($CH_3OC(O)CH_2CH_2$), 54.17, 54.28 (**CH_3**OC(O)CH_2), 54.17 (CH glutyl), 59.31 (1'-C), 69.50 (5'-C), 115.42 (5-C), 120.48, 120.51, 120.55, 120.58 (*o*-Ph), 125.39 (*p*-Ph), 130.09, 130.22 (*m*-Ph), 131.55, 131.60 (3'-C), 136.13 (8-C), 1136.68, 136.77 (2'-C), 150.98, 151.05, 151.13 (6-C), 151.76 (*i*-Ph), 156.65 (4-C), 160.99, 161.02, 161.08, 161.12 (2-C), 173.33, 173.43 (C(O) x 2 glutyl).
ES+ m/e 600.2216 (MH^+, $C_{27}H_{35}N_7O_7P$ requires 600.2335).
HPLC t_R 27.25 min (0% CH_3CN (0 min), 80% CH_3CN (35 min), 80% CH_3CN (45 min), 0% CH_3CN (55 min)).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl (methoxy-α-ethyl-L-glycinyl phosphate) CF1783

[0252] This was prepared by Standard Procedure 4.44% yield.
δ_P 4.10.
δ_H 0.59 (2H, m, CH_aH_b, CH_a,H_b, cyclopropyl), 0.83 (5H, br m, CH_aH_b, CH_a,H_b, cyclopropyl, **CH_3**-CH_2), 1.68 (3H, m, CH_3-**CH_2**, 6'-**H_a**), 2.69 (1H, m, 6'-H_aH_b), 2.91 (1H, m, 4'-H), 3.06 (1H, m, CH cyclopropyl), 3.58 (3H, d, J 3.0, MeO), 3.90 (2H, m, NH glycinyl, CH glycinyl), 4.07 (2H, m, 5'-H), 5.02 (2H, br s, NH_2), 5.42 (1H, m, 1'-H), 5.75 (1H, m, 3'-H), 5.98 (1H, m, 2'-H), 6.03 (1H, m, NH cyclopropyl), 7.18 (5H, m, Ph-H), 7.41 (1H, br d, 8H).
δ_C 7.76 (CH_2-cyclopropyl x 2), 9.68, 9.76 (**CH_3**CH_2), 24.12 (CH-cyclopropyl), 28.05 (CH_3**CH_2**), 35.01 (6'-C), 46.02, 46.13 (4'-C), 52.70, 52.73 (CH_3O), 56.02 (1'-C), 59.25 (CH-ala), 69.38 (5'-C), 116.10 (5-C), 120.48, 120.50, 120.55, 120.57 (*o*-Ph), 125.27 (*p*-Ph), 130.04 (*m*-Ph), 131.51 (3'-C), 135.86 (8-C), 136.86 (2'-C), 151.08, 151.13, 151.22 (6-C, i-Ph), 156.67 (4-C), 160.40 (2-C), 173.84, 173.87, 173.92 (C(O) alaninyl).
ES+ m/e 564.2094 (M[Na]$^+$, $C_{25}H_{32}N_7O_5NaP$ requires 564.2100).
HPLC t_R 16.82, 16.84 min (0% CH_3CN (0 min), 80% CH_3CN (15 min), 80% CH_3CN (25 min), 0% CH_3CN (35 min)).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl (methoxy-α-phenyl(RS)glycinyl phosphate) CF1784

[0253] This was prepared by Standard Procedure 4.46% yield.
δ_P 3.18, 3.28, 3.42, 4.29.
Proton and Carbon NMR gave complex spectra, consistent with the racemised product.
ES+ m/e 612.2086 ($M[Na]^+$, $C_{29}H_{32}N_7O_5NaP$ requires 612.2100).
HPLC t_R 17.63, 18.50 min (0% CH_3CN (0 min), 80% CH_3CN (15 min), 80% CH_3CN (25 min), 0% CH_3CN (35 min)). (1:1.08 racemisation by HPLC)

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl (methoxy-a-butyl-L-glydnyl phosphate) CF1786

[0254] This was prepared by Standard Procedure 4.51% yield*.
δ_P 4.10, 4.16.
δ_H 0.51 (2H, m, CH_aH_b, CH_a,H_b, cyclopropyl), 0.72 (5H, br m, CH_aH_b, CH_a,H_b, cyclopropyl, $\mathbf{CH_3}$-CH_2), 1.18 (4H, m, CH_3-$\mathbf{CH_2}$-$\mathbf{CH_2}$-), 1.54 (3H, m, CH_2-$\mathbf{CH_2}$-O, 6'-$\mathbf{H_aH_b}$), 2.73 (1H, m, 6'-H_aH_b), 2.93 (1H, m, 4'-H), 3.09 (1H, m, CH cyclopropyl), 3.52 (1H, m, CH glycinyl), 3.62 (3H, s, MeO), 3.87 (1H, m, NH glycinyl), 4.12 (2H, m, 5'-H), 4.75 (2H, br s, NH_2), 5.45 (1H, m, 1'-H), 5.79 (2H, br s, NH-cyclopropyl, 3'-H), 6.00 (1H, m, 2'-H), 7.20 (5H, m, Ph-H), 7.42 (1H, br d, 8H).
δ_C 7.76 (CH_2-cyclopropyl x 2), 14.23 ($\mathbf{CH_3}CH_2$), 22.56 ($CH_3\mathbf{CH_2}$), 24.14 (CH-cyclopropyl), 27.43, 27.50 ($CH_3CH_2\mathbf{CH_2}$), 34.50, 34.58 ($CH_2\mathbf{CH_2}O$), 35.01 (6'-C), 46.02, 46.12 (4'-C), 52.66, 52.68 (CH_3O), 54.87, 54.94 (1'-C), 59.20 (CH-ala), 69.30, 69.37 (5'-C), 115.18 (5-C), 120.29, 120.42, 120.50, 120.57 (*o*-Ph), 125.21 (*p*-Ph), 130.00 (*m*-Ph), 131.51, 131.54 (3'-C), 135.86 (8-C), 136.71, 136.76 (2'-C), 151.12, 151.16, 151.20, 151.25 (6-C, *i*-Ph), 156.73 (4-C), 160.49, 160.96 (2-C), 174.19, 174.26 (C(O) glycinyl).
ES+ m/e 592.2428 ($M[Na]^+$, $C_{27}H_{36}N_7O_5NaP$ requires 592.2413).
HPLC t_R 1834, 18.41, min and 16.64 min (6:1) (0% CH_3CN (0 min), 80% CH_3CN (35 min), 80% CH_3CN (45 min), 0% CH_3CN (55 min)).
* Note: compound isolated as 6:1 (S:R) stereoisomeric mixture at the amino acid residue α-carbon. Additional resonances in the ^{31}P NMR spectra are noted at 4.35 and 5.18, corresponding to the minor configuration (R) amino acid residue containing diastereoisomers.

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl (methoxy-α-propyl-L-glycinyl phosphate) CF1785

[0255] This was prepared by Standard Procedure 4.50% yield.
δ_P 4.14,4.21.
δ_H 0.62 (2H, m, CH_aH_b, CH_a,H_b, cyclopropyl), 0.86 (5H, br m, CH_aH_b, CH_a,H_b, cyclopropyl, $\mathbf{CH_3}$-CH_2), 1.32 (2H, m, CH_3-$\mathbf{CH_2}$-). 1.63 (3H, m, CH_3-$\mathbf{CH_2}$, 6'-$\mathbf{H_aH_b}$), 2.79 (1H, m, 6'-H_aH_b), 3.03 (1H, m, 4'-H), 3.18 (1H, m, CH cyclopropyl), 3.71 (3H, d, J 3.0, MeO), 3.97 (1H, m, CH glycinyl), 4.15 (3H, m, 5'-H, NH glycinyl), 5.09 (2H, br s, NH_2), 5.55 (1H, m, 1'-H), 5.90 (1H, m, 3'-H), 6.08 (2H, m, 2'-H, NH cyclopropyl), 7.23 (5H, m, Ph-H), 7.52 (1H, br d, 8H).
δ_C 7.55 (CH_2-cyclopropyl x 2), 13.98 ($\mathbf{CH_3}CH_2$), 18.62, 18.70 ($CH_3\mathbf{CH_2}$), 24.15 (CH-cyclopropyl), 35.00 (6'-C), 36.89, 36.96 ($CH_2\mathbf{CH_2}O$), 46.02, 46.12 (4'-C), 52.68 (CH_3O), 54.70, 54.77 (1'-C), 59.21 (CH-ala), 69.31, 69.38 (5'-C), 115.24 (5-C), 120.45, 120.51, 120.57 (*o*-Ph), 125.22 (*p*-Ph), 130.01 (*m*-Ph), 131.54 (3'-C), 135.89 (8-C), 136.72, 136.78 (2'-C), 151.11, 151.16, 151.20, 151.25 (6-C, *i*-Ph), 156.72 (4-C), 160.45, 160.95 (2-C), 174.18, 174.25 (C(O) alaninyl).
ES+ m/e 578.2259 ($M[Na]^+$, $C_{26}H_{34}N_7O_5NaP$ requires 578.2257).
HPLC t_R 17.57 min (0% CH_3CN (0 min), 80% CH_3CN (35 min), 80% CH_3CN (45 min), 0% CH_3CN (55 min)).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-((*p*-(2",2"-dimethoxypropionic acid methyl ester)-phenyl)methoxy-L-alaninyl phosphate) CF1671

[0256] This was prepared by Standard Procedure 4.24 % yield.
δ_P 3.72, 3.84.
δ_H 0.56 (2H, m, CH_aH_b, CH_a,H_b, cyclopropyl), 0.79 (2H, m, CH_aH_b, CH_a,H_b, cyclopropyl), 1.30 (3H, m, $\mathbf{CH_3}$ alaninyl), 1.63 (1H, m, 6'-$\mathbf{H_aH_b}$), 2.70 (1H, m, 6'-H_aH_b), 2.95 (1H, br s, 4'-H), 3.07 (3H, m, CH cyclopropyl, Ph-CH_2-), 3.26 (6H, s, $(OMe)_2$), 3.52 (3H, s, $C(OMe)_2COOMe$), 3.61 (3H, s, COOMe alaninyl), 3.84 - 4.08 (4H, m, CH alaninyl, NH alaninyl, 5'-H), 4.99 (2H, br s, NH_2), 5.46 (1H, br m, 1'-H), 5.81 (1H, br s, 3'-H), 6.02 (2H, m, 3'-H, NH-cyclopropyl), 6.02 (1H, m, 2'-H), 7.02 (4H, m, Ph-H), 7.45 (1H, br d, 8H).
δ_c 7.77 (CH_2-cyclopropyl x 2), 21.37 (Me alaninyl), 24.01 (CH-cyclopropyl), 34.89 (6'-C), 39.55 (Ph-CH_2), 45.97, 46.09

(4'-C), 50.53 ((**MeO**)$_2$, CH_3OO alaninyl), 52.65 (C(OMe)$_2$**COOMe**), 59.28 (1'-C), 69.29 (5'-C), 103.27 (**C**(OMe)$_2$), 120.31, 120.38 (o-Ph), 122.94 (*p*-Ph), 131.35 (*m*-Ph), 131.39 (3'-C), 136.79 (8-C, 2'-C), 150.14, 150.05 (*i*-Ph, 6-C), 152.12 (4-C), 160.24 (2-C), 169.08 (C(OMe)$_2$COOMe), 174.36, 174.46 (**C**(O) alaninyl).
ES+ m/e 696.2531 ([M]$^+$, $C_{30}H_{40}N_7O_9NaP$ requires 696.2523).
HPLC t_R 29.02 min (0% CH_3CN (0 min), 80% CH_3CN (35 min), 80% CH_3CN (45 min), 0% CH_3CN (55 min)).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-((*p*-methoxyphenyl) methoxy-L-alaninyl phosphate) CF1815

[0257] This was prepared by Standard Procedure 4.23% yield.
δ_P 4.23, 4.28.
δ_H 0.72 (2H, m, CH_aH_b, $CH_{a'}H_{b'}$ cyclopropyl), 1.0 (2H, m, CH_aH_b, $CH_{a'}H_{b'}$ cyclopropyl), 1.48 (3H, m, CH_3 alaninyl), 1.82 (1H, m, 6'-H_aH_b), 2.80 (1H, m, 6'-H_aH_b), 3.11 (1H, br s, 4'-H), 3.25 (1H, m, CH cyclopropyl), 3.67 (1H, m, NH alaninyl), 3.77 (3H, s, COOMe alaninyl), 3.89 (3H, s, MeO-Ar), 4.14 (1H, m, CH alaninyl), 4.30 (2H, m, 5'-H), 4.94 (2H, br s, NH_2), 5.65 (1H, br m, 1'-H), 5.83 (1H, br s, NH-cyclopropyl), 6.00 (1H, m, 3'-H), 6.17 (1H, m, 2'-H), 6.92 (2H, m, *m*-Ar), 7.23 (2H, m, *o*-Ar), 7.63 (1H, s, 8H).
δ_C 7.81 (CH_2-cyclopropyl x 2), 21.46, 21.52 (Me alaninyl), 24.00 (CH-cyclopropyl), 34.96 (6'-C), 46.04, 46.14 (4'-C), 50.64 (CH_3OO alaninyl), 52.89 (CH-alaninyl), 56.02 (CH_3O-Ar), 59.28 (1'-C), 69.30 (5'-C), 114.98 (*m*-Ph, 5-C), 121.42, 121.46, 121.52 (*o*-Ph), 131.52, 131.56 (3'-C), 135.98, (2'-C), 136.76, 136.87 (*i*-Ph), 144.61 (8-C), 156.71 (4-C), 157.01 (*p*Ar), 161.40, 160.99 (2-C), 174.39, 174.50 (C(O) alaninyl).
HPLC t_R 16.28 (0% CH_3CN (0 min), 80% CH_3CN (15 min), 80% CH_3CN (25 min), 0% CH_3CN (35 min)).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-((*p*-propoxyphenyl) methoxy-L-alaninyl phosphate) CF1816

[0258] This was prepared by Standard Procedure 4.56% yield.
δ_P 4.33, 4.41.
δ_H 0.62 (2H, m, CH_aH_b, $CH_{a'}H_{b'}$ cyclopropyl), 0.82 (2H, m, CH_aH_b, $CH_{a'}H_{b'}$ cyclopropyl), 1.03 (3H, t, J 6.0, **CH_3**-CH_2), 1.39 (3H, m, CH_3 alaninyl), 1.66 (1H, m, 6'-H_aH_b), 1.80 (2H, h, J 6.0, CH_3-**CH_2**), 2.79 (1H, m, 6'-H_aH_b), 3.01 (1H, br s, 4'-H), 3.12 (1H, m, CH cyclopropyl), 3.72 (3H, s, COOMe alaninyl), 3.89 (2H, t, J 6.0, CH_2-O), 4.04 (2H, m, CH alaninyl, NH alaninyl), 4.17 (2H, m, 5'-H), 5.10 (2H, br s, NH_2), 5.52 (1H, br m, 1'-H), 5.51 (1H, br s, NH-cyclopropyl), 5.89 (1H, m, 3'-H), 6.04 (1H, m, 2'-H), 6.81 (2H, m, *m*Ar), 7.11 (2H, m, *o*-Ar), 7.51 (1H, s, 8H).
δ_C 7.77 (CH_2-cyclopropyl x 2), 10.91 (**CH_3**-CH_2), 21.39, 21.46 (Me alaninyl), 22.97 (CH_3-**CH_2**), 24.14 (CH-cyclopropyl), 34.96 (6'-C), 46.02, 46.13 (4'-C), 50.57, 50.65 (CH_3OO alaninyl), 52.85, 52.87 (CH-alaninyl), 53.89 0, 59.25 (1'-C), 69.16, 69.24, 69.33 (5'-C), 70.30 (CH_2-O), 115.24, 115.26 (5-C), 115.57 (m-Ph), 121.37, 121.40, 121.43, 121.46 (*o*-Ph), 131.51, 131.57 (3'-C), 135.93, (2'-C), 136.77, 136.85 (*i*-Ph), 144.47, 144.55 (8-C), 156.54, 156.73 (4-C), 160.45 (*p*-Ar), 160.91 (2-C), 174.48, 174.59 (**C**(O) alaninyl).
HPLC t_R min (0% CH_3CN (0 min), 80% CH_3CN (15 min), 80% CH_3CN (25 min), 0% CH_3CN (35 min)).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[4-hydroxyacetophenone-(methoxy-L-alaninyl)]-phosphoramidate Cf 1794

[0259] This was prepared by Standard procedure 4. The crude residue was purified twice by column chromatography, using MeOH:CHCl3 (3%:97) and MeOH:EtOAc (5:95) as eluent, to give the product as a white foam (30 mg, 17 mmol, 15 %).
δ_P 3.496.
δ_H 0.66 (m,2H,CH2-cPr), 0.85 (m,2H,CH2-cPr), 1.33 (m, 3H, CH3-CH), 1.7 (m, 1H, H'6), 2.53 (s, 3H, CH3-COPh), 2.8 (m, 1H, H'6), 2.9 (m, 1H, CH-cPr), 3.1 (m, 1H, H'4), 3.6 (s, 3H, CH3-O), 3.9 (m, 1H, CH3-CH), 4.1 (m, 2H, H'5), 4.9 (m, 2H, NH2), 5.5 (m, 1H,H'1), 5.85 (m, 1H, H'3), 6.1 (m, 2H, H'2,NHcPr) 7.2 (dd, 2H, o-Ar), 7.5 (m, 1H, H8), 7.8 (dd, 2H, *p*-Ar)
δ_C 6.371 (CH2cPr), 20 (CH-CH3aa), 21.671 (NHCH3), 25 (CH3CO), 33.458 (C6), 44.55 (C'4),49.5 (CHaa), 51.4 (OCH3), 57.9 (C'1), 67.9 (C'5), 113.787 (C5), 120 (*o*-Ar), 122.22 (*p*-Ar), 128.743 (*m*-Ar), 130 (C'3), 134.53 (C'2), 135.31 (C8), 150.31 (*i*-Ar), 155.18 (C6), 156.342 (C2), 158.8 (C4), 173.004 (COOCH3), 198 (CO-Ar).
HPLC t_r: 15.976 min (0% CH_3CN (0 min), 80% CH_3CN (15 min), 80% CH_3CN (25 min), 0% CH_3CN (35 min)).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[4n-butylphenyl-(methoxy-L-alaninyl)]-phosphate Cf 1795

[0260] The crude residue was purified twice by column chromatography, using MeOH:CHCl3 (3%:97) and MeOH: CH_2Cl_2 (5:95) as eluent, to give the product as a white foam (15 mg, 0.025 mmol, 4 %),
δ_P 3.93-4.00.
δ_H 0.66 (m,2H,CH2-cPr), 0.85 (m,2H,CH2-cPr), 1.1 (m,3H, CH_3-CH_2), 1.2 (m,4H, CH_2-CH_2), 1.33 (m, 3H, CR3-CR), 1.7 (m, 1H, H'6), 2.5 (m, 2H, CH_2-Ar), 2.8 (m, 1H, H'6), 2.9 (m, 1H, CH-cPr), 3.1 (m, 1H, H'4), 3.6 (s, 3H, CH3-O), 3.9 (m, 1H, CH3-CH), 4.1 (m, 2H, H'5), 4.9 (m, 2H, NH2), 5.5 (m, 1H,H'1), 5.85 (m, 1H, H'3), 6.1 (m, 2H, H'2,NHcPr), 7.2 (dd, 2H, *o*-Ar), 7.5 (m, 1H, H8), 7.8 (dd, 2H, *p*-Ar).
δ_C 6.371 (CH2cPr), 14.345 (CH_3-CH_2), 21.49 (CH-CH3aa), 22.66 (CH_2-CH_3), 21.671 (NHCH3), 30.127 (CH2-CH2-CH2), 33.458 (C'6), 34.047.(CH2-Ar), 44.55 (C'4), 49.5 (CHaa), 51.4 (OCH3), 57.9 (C'1), 67.9 (C5), 113.787 (C5), 120 (*o*-Ar), 122.22 (*p*-Ar), 128.743 (*m*-Ar), 130 (C'3), 134.53 (C'2), 135.31 (C8),146.58 (*i*-Ar) 155.18 (C6), 156.342 (C2), 158.8 (C4), 173.004 (COOCH3)
HPLC t_r: 19.591 min (0% CH_3CN (0 min), 80% CH_3CN (15 min), 80% CH_3CN (25 min), 0% CH_3CN (35 min)).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenylphenyl-(methoxy-L-alaninyl)]-phosphate Cf 1788

[0261] The crude residue was purified three times by column chromatography, using MeOH:CHCl3 (3:97) and MeOH: CH_2Cl_2 (5:95) and MeOH:AcOEt (3:97) as eluent, to give the product as a yellow foam (35 mg, 0.058 mmol, 8 %).
δ_P 3.94-3.96.
δ_H 0.66 (m,2H,CH2-cPr), 0.85 (m,2H,CH2-cPr), 1.33 (m, 3H, CH3-CH), 1.7 (m, 1H, H'6), 2.8 (m, 1H, H'6), 2.9 (m, 1H, CH-cPr), 3.25 (m, 1H, H'4), 3.6 (s, 3H, CH3-O), 4.1 (m, 1H, CH3-CH), 4.25 (m, 2H, H'5), 4.9 (m, 2H, NH2), 5.5 (m, 1H, H'1), 5.85 (m, 1H, H'3), 6.15 (m, 2H, H'2,NHcPr), 7.35 (m, 9H, Ar), 7.6 (m, 1H, H8).
δ_C 6.371 (CH2cPr), 21.49 (CH-CH3aa), 21.671 (NHCH3), 33.458 (C'6), 46.14 (C'4), 50.671 (CHaa), 52.9 (OCH3), 59.9 (C'1), 65.9 (C'5), 115.787 (C5), 120 (*o*-Ar), 122.22 (*p*Ar), 128.743 (*m*-Ar), 130 (C'3), 134.53 (C'2), 135.31 (C8), 145.25 (*i*-Ar), 155.18 (C6), 156.342 (C2), 158.8 (C4), 173.004 (COOCH3).
HPLC t_r: 19.147 min (0% CH_3CN (0 min), 80% CH_3CN (15 min), 80% CH_3CN (25 min), 0% CH_3CN (35 min)).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenoxyphenyl-(methyoxy-L-alaninyl)]-phosphate Cf 1787

[0262] The crude residue was purified twice by column chromatography, using MeOH:CHCl3 (3:97) and MeOH: CH_2Cl_2 (5:95) as eluent, to give the product as a yellow foam (35 mg, 0.058 mmol, 8 %).
δ_P 4.212-4.184.
δ_H 0.66 (m,2H,CH2-cPr), 0.85 (m,2H,CH2-cPr), 1.33 (m, 3H, CH3-CH), 1.7 (m, 1H, H'6), 2.8 (m, 1H, H'6), 2.9 (m, 1H, CH-cPr), 3.25 (m, 1H, H'4), 3.6 (s, 3H, CH3-O), 4.1 (m, 1H, CH3-CH), 4.25 (m, 2H, H'5), 4.9 (m, 2H, NH2), 5.5 (m, 1H, H'1), 5.85 (m, 1H, H'3), 6.15 (m, 2H, H'2,NHcPr), 7.35 (m, 9H, Ar), 7.6 (m, 1H, H8).
δ_C 6.371 (CH2cPr), 21.49 (CH-CH3aa), 21.671 (NHCH3), 33.458 (C'6), 46.14 (C'4), 50.671 (CHaa), 52.9 (OCH3), 59.9 (C'1), 65.9 (C'5), 115.787 (C5), 120 (*o*-Ar), 122.22 (*p*-Ar_2), 128.743 (*m*-Ar), 130 (C'3), 134.53 (C'2), 135.31 (C8), 153.83 (*i*-Ar_2, *m*-Ar_1), 155.18 (C6), 156.342 (C2), 158.8 (C4), 173.004 (COOCH3).
HPLC t_r: 18.830 min (0% CH_3CN (0 min), 80% CH_3CN (15 mm), 80% CH_3CN (25 min), 0% CH_3CN (35 min)).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl methoxy-α,α-cyclopentylglycinyl] phosphate Cf1763

[0263] This was prepared by Standard procedure 4 in 77% yield.
^{31}P ($CDCl_3$) 3.02, 3.09
^1H ($CDCl_3$) 0.56-0.61 (2H,m, CH_2 (cpro)), 0.81-0.89 (2H, m, CH_2 (cpro)), 1.58-1.78 (5H, m, $CCH_2CH_2CH_2CH_2C$, and H6'), 1.87-2.18 (4H, m, $CCH_2CH_2CH_2CH_2C$), 2.64-2.74 (1H, m, H6'), 2.83-3.09 (2H, m, CH(cpro), H4'), 3.60-3.62 (3H, s, OCH_3(ala)), 4.04-4.19 (2H, m, H5'), 5.20 (2H, bs, NH_2), 5.42-5.47 (1H, m, H1'), 5.77-5.83 (1H, m, H3'), 5.98-6.02 (1H, m, H2'), 6.20 (NH(cpro)), 7.06-7.27 (5H, m, Ar), 7.42-7.48 (1H, s, H8).
^{13}C ($CDCl_3$) 8.02 (CH_2(cpro)), 24.37, 24.41 ($CCH_2CH_2CH_2CH_2C$), 34.73 (C6'), 38.48, 38.68, 38.79, 38.87 ($CCH_2CH_2CH_2CH_2C$), 46.05, 46.15 (C4'), 52.99 (OCH_3(ala)), 59.56, 59.60 (C1'), 67.16 (C (aa), 69.28, 69.37 (C5'), 114.76 (C5), 120.46, 120.52 (o-Ph), 125.22 (p-Ph), 130.04 (m-Ph), 131.19 (C3'), 136.72 (C8), 137.13,137.20 (C2'), 151.27, 151.31, 151.36, 151.40 (C6), 155.56 (C4), 158.95 (C2), 175.96, 176.00 (CO).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl methoxy-a,a-cyclohexylglycinyl] phosphate Cf1764

[0264] This was prepared by Standard procedure 4 in 15% yield.
^{31}P ($CDCl_3$) 2.89, 3.00
^{1}H ($CDCl_3$) 0.74 (2H,m, CH_2 (cpro)), 1.01-1.03 (2H, m, CH_2 (cpro)), 1.29-2.23 (11H, m, $CCH_2CH_2CH_2CH_2CH_2C$, and H6'), 2.72-2.83 (1H, m, H6'), 3.17 (1H, bs, CH(cpro)), 3.35-3.43 (1H, m, H4'), 3.69-3.70 (3H, s, OCH_3(aa)), 4.16-4.29 (2H, m, H5'), 5.52-5.66 (1H, m, H1'), 5.79 (1H, bs, NH(cpro)), 5.85-5.90 (1H, m, H3'), 6.08-6.10 (1H, m, H2'), 7.15-7.35 (5H, m, Ar), 7.37-7.63 (1H, d, H8).
^{T3}C ($CDCl_3$) 8.30 (CH_2(cpro)), 21.49, 21.68, 21.84, 22.02, 22.11 ($CCH_2CH_2CH_2CH_2CH_2C$), 25.14, 25.47, 25.72 ($CCH_2CH_2CH_2CH_2CH_2C$), 34.37, 34.59 (C6'), 46.06, 46.16 (C4'), 52.75, 53.12 (OCH_3(aa)), 59.95, 60.19 (C1'), 69.22 (C5'), 120.41, 120.47 (o-Ph), 125.22 (p-Ph), 130.04 (m-Ph), 130.72, 130.82 (C3'), 137.41 (C8), 137.56 (C2'), 151.33, 151.43 (C6), 175.37 (CO).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O -[phenyl methoxy-α,α-cyclopropylglycinyl] phosphate Cf1762

[0265] This was prepared by Standard procedure 4 in 69% yield.
^{31}P ($CDCl_3$) 3.84
^{1}H ($CDCl_3$) 0.68(2H,m, CH_2 (cpro)), 0.90-0.92 (2H, m, CH_2 (cpro)), 1.16-1.49 (4H, m, CCH_2CH_2C(aa)), 1.66-1.72 (1H, m, H6'), 2.72-2.82 (1H, m, H6'), 3.08-3.15 (2H, m, CH(cpro), H4'), 3.61-3.63 (3H, d, OCH_3(aa)), 4.24-4.26 (2H, m, H5'), 5.24 (2H, bs, NH_2), 5.53 (1H, bs, H1'), 5.87(1H, m, H3'), 6.07 (1H, m, H2'), 6.42-6.45 (1H, bs, NH(cpro)), 7.15-7.35 (5H, m, Ar), 7.56-7.61 (1H, d, H8).
^{13}C ($CDCl_3$) 7.92 (CH_2(cpro)), 18.38 (CH_2 (aa)), 35.20 (C6'), 52.88 (OCH_3(aa)), 59.45 (C1'), 69.32 (C5'), 120.52 (o-Ph), 125.29 (p-Ph), 130.04 (m-Ph),137.03 (C2'), 151.13 (C6), 160.96, 160.98 (C2), 174.35 (CO).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[p-(methoxycarbonyl) phenyl methoxy-L-alaninyl] phosphate Cf1766

[0266] This was prepared by Standard procedure 4 in 37% yield.
^{31}P ($CDCl_3$) 3.54, 3.58
^{1}H ($CDCl_3$) 0.66-0.69 (2H,m, CH_2 (cpro)), 0.88-0.94 (2H, m, CH_2 (cpro)), 1.38-1.43 (3H, t, CH_3(ala)), 1.70-1.81 (1H, m, H6'), 2.76-2.89 (1H, m, H6'), 3.07 (1H, m, CH(cpro)), 3.21 (1H, m, H4'), 3.71-3.73 (3H, d, OCH_3(ala)), 3.94 (3H, s, $COOCH_3$), 3.98-4.12 (1H, m, CH(ala)), 4.20-4.31 (2H, m, H5'), 5.19 (2H, bs, NH_2), 5.54-5.57 (1H, m, H1'), 5.91-5.96 (1H, m, H3'), 6.09-6.14 (1H, m, H2'), 6.21 (1H, bs, NH(cpro)), 7.27-7.32 (2H, m, ArO,2H), 7.53-7.54 (1H, d, H8), 8.02-8.06 (2H, m, COAr,2H).
^{13}C ($CDCl_3$) 7.75 (CH_2(cpro)), 21.22, 21.29, 21.46 (CH_3(ala)),24.16 (NHCH), 34.83 (C6'), 45.97, 46.07 (C4'), 50.59 (CH(ala)), 52.57, 59.32 (OCH_3 (ala), OCH_3(Ph)), 59.27, 59.32 (C1'), 69.43 (C5'), 115.07, 115.11 (C5), 120.28, 120.31, 120.34, 120.38 (o-Ph), 127.07 (p-Ph), 131.58, 131.66 (m-Ph), 131.88 (C3'), 135.94, 136.04 (C2'), 136.61, 136.73 (C8), 151.31 (C6), 156.52 (C2), 160.97 (C4), 171.57 (CO), 174.30, 174.39 (CO).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[p-(trifluoromethylthio) phenyl methoxy-L-alaninyl] phosphate Cf 1769

[0267] This was prepared by Standard procedure 4 in 34% yield.
^{31}P ($CDCl_3$) 3.67, 3.88
^{1}H ($CDCl_3$) 0.81 (2H,bs, CH_2 (cpro)), 1.06-1.08 (2H, m, CH_2 (cpro)), 1.50-1.54 (3H, t, CH_3(ala)), 1.83-1.93 (1H, m, H6'), 2.87-2.99 (1H, m, H6'), 3.23-3.31 (1H, m, CH(cpro)), 3.82-3.84 (3H, d, OCH_3(ala)), 4.14-4.15 (1H, m, CH(ala)), 4.32-4.40 (2H, m, H5'), 5.65 (3H, bs, H1', NH_2), 6.01-6.04 (1H, m, H3'), 6.19-6.23 (1H, m, H2'), 6.64 (1H, bs, NH(cpro)), 7.37-7.43(2H, m, Ar), 7.67 (1H, d, H8), 7.73-7.76 (2H, m, Ar).
^{T3}C ($CDCl_3$) 8.16 (CH_2(cpro)), 21.39, 21.45 (CH_3(ala)), 34.45 (C6'), 46.09 (C4'), 50.66 (CH(ala)), 53.01 (OCH_3 (ala)), 59.87 (C1'), 69.34 (C5'), 77.47, 77.67 (CF_3S ?), 121.64, 121.69 (o-Ph), 127.07 (p-Ph), 136.99, 137.14 (C2'), 138.56 (C8), 153.36, 153.45 (C6), 160.93 (C4), 174.27 (CO).

(1 S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[p-(2-methoxyvinyl) phenyl methoxy-L-alaninyl] phosphate Cf 1767

[0268] This was prepared by Standard procedure 4 in 38% yield.

^{31}P ($CDCl_3$) 3.70, 3.74

^{1}H ($CDCl_3$) 0.58-0.61 (2H,bs, CH_2 (cpro)), 0.81-0.85 (2H, m, CH_2 (cpro)), 1.30-1.36 (3H, t, CH_3(ala)), 1.61-1.72 (1H, m, H6'), 2.33 (3H, s, CH_3CO), 2.70-2.79 (1H, m, H6'), 2.99 (1H, bs, CH(cpro)), 3.13(1H, bs, H4'), 3.64-3.65 (3H, d, OCH_3(ala)), 3.92-4.01 (1H, m, CH(ala)), 4.11-4.21 (2H, m, H5'), 5.14 (3H, bs, H1', NH_2), 5.47-5.49 (1H, m, H1'), 5.82-5.87 (1H, m, H3'), 6.01-6.06 (1H, m, H2'), 6.12 (1H, bs, NH(cpro)), 6.57-6.63 (1H, dd, CH3COCH=CH), 7.14-7.46 (6H, m, H8, Ar, CH_3COCH=).

^{13}C ($CDCl_3$) 7.95 (CH_2(cpro)), 21.45 (CH_3(ala)), 28.02 (CH_3CO), 34.69 (C6'), 46.11 (C4'), 50.64 (CH(ala)), 52.99 (OCH_3 (ala)), 59.53 (C1'), 121.03, 121.10, 121.17 (o-Ph), 127.39 (p-Ph), 130.13 (CH_3COCH=CH), 131.44, 131.55 (C3'), 136.76 (C2'), 142.59 (CH_3COCH=CH), 152.72 (C6), 174.26, 174.36 (CO(ala)), 198.70 ($COCH_3$).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[p-(2-phenylcarbonylvinyl)phenyl methoxy-L-alaninyl] phosphate Cf 1771

[0269] This was prepared by Standard procedure 4 in 26% yield.

^{31}P ($CDCl_3$) 3.75, 3.79

^{1}H ($CDCl_3$) 0.61-0.66 (2H,m, CH_2 (cpro)), 0.85-0.91 (2H, m, CH_2 (cpro)), 1.39-1.44 (3H, m, CH_3(ala)), 1.67-1.86 (1H, m, H6'), 2.77-2.87 (1H, m, H6'), 3.04-3.05 (1H, bs, CH(cpro)), 3.19-3.21 (1H, bs, H4'), 3.72-3.73 (3H, d, OCH_3(ala)), 4.02-4.13 (1H, m, CH(ala)), 4.19-4.29 (2H, m, H5'), 5.17 (3H, bs, H1', NH_2), 5.53-5.58 (1H, m, H1'), 5.90-5.95 (1H, m, H3'), 6.09-6.15 (2H, m, H2', NH(cpro)), 7.24-8.08 (12H, m, Ar-, CH=CH,-Ar-, H8).

^{13}C ($CDCl_3$) 7.85 (CH_2(cpro)), 21.35, 21.41, 21.48 (CH_3(ala)), 24.22 (CH(NH)), 34.80 (C6'), 46.01 (C4'), 50.67 (CH (ala)), 52.97 (OCH_3 (ala)), 59.37 (C1'), 69.40 (C5'), 115.07 (C5), 121.01, 121.07, 121.14 (o-Ph), 128.92, 129.06 (p-Ph), 133.27 (C3'), 136.13, 136.23 (C2'), 138.53 (C8), 152.77, 152.86 (C6), 156.31 (C2), 160.97, 160.99 (C4), 174.31, 174.41 (CO(ala)), 190.76 (CO (Ar)).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[p-(2,2-dicyanovinyl) phenyl methoxy-L-alaninyl] phosphate Cf 1768

[0270] This was prepared by Standard procedure 4 in 10% yield.

^{31}P ($CDCl_3$) 4.54, 4.65

^{1}H ($CDCl_3$) 0.61-0.66 (2H,m, CH_2 (cpro)), 0.85-0.91 (2H, m, CH_2 (cpro)), 1.34-1.41 (3H, m, CH_3(ala)), 1.67-1.83 (1H, m, H6'), 2.77-2.88 (1H, m, H6'), 2.95-2.97 (1H, m, CH(cpro)), 3.23 (1H, bs, H4'), 3.68-3.70 (3H, d, OCH_3(ala)), 3.99-4.03 (1H, m, CH(ala)), 4.22-4.32 (2H, m, H5'), 5.49-5.53 (1H, m, H1'), 5.99-6.03 (1H, m, H3'), 6.16-6.22 (1H, m, H2'), 6.94-6.97 (1H, dd, Ar-CH=CH), 7.36-7.41 (Ar), 7.64-7.65 (1H, d, H8), 7.92-8.16 (Ar).

^{13}C ($CDCl_3$) 6.56 (CH_2(cpro)), 19.85 (CH_3(ala)), 23.33 (CH(cpro)), 34.23 (C6'), 46.07 (C4'), 50.47, 50.53 (OCH_3 (ala)), 51.78 (CH(ala)), 59.51 (C1'), 69.19, 69.29 (C5'), 113.84, 114.08 (C5), 121.14, 121.21, 121.27 (o-Ph), 128.49 (p-Ph), 130.74, 130.85 (m-Ph), 132.84 (C3'), 136.01 (C2'), 136.88, 136.99 (C8), 156.47 (C2), 160.99, 161.03 (C4), 174.27 (CO).

(1S,4R)-4-(2-amino-6-cyclopropylamino-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[o-(carboxylate ethyl ester)phenyl methoxy-L-alaninyl] phosphate Cf1798

[0271] This was prepared by Standard procedure 4 in 24% yield.

^{31}P ($CDCl_3$) 4.03, 4.16

^{1}H ($CDCl_3$) 0.64-0.70 (2H,m, CH_2 (cpro)), 0.92-0.93 (2H, d, CH_2 (cpro)), 1.38-1.47 (6H, m, CH_3(ala), CH_3CH_2O), 1.73-1.83 (1H, m, H6'), 2.78-3.24 (3H, m, H6', H4', CH(cyclo)), 3.64-3.72 (3H, s, OCH_3(ala)), 4.08-4.20 (1H, m, CH (ala)), 4.23-4.45 (4H, m, H5', CH_2CH_3), 5.21 (2H, bs, NH_2), 5.55-5.60 (1H, m, H1'), 5.89-5.93 (1H, m, H3'), 6.13-6.18 (1H, m, H2'), 7.23-7.61 (1H, m, H8), 7.88-7.92 (1H, d, Ar).

^{13}C ($CDCl_3$) 7.95 (CH_2(cpro)), 14.65 (CH_3CH_2), 21.33, 21.39, 21.68, 21.74 (CH_3(ala)), 24.30 (NHCH), 34.80 (C6'), 46.04, 46.14 (C4'), 50.49 (CH(ala)), 52.74, 52.83 (OCH_3 (ala)), 59.45 (C1'), 61.76, 61.82 (CH_2CH_3), 69.43, 69.51, 69.64 (C5'). 114.92 (C5), 122.93, 123.09, 123.60, 123.67125.26 (Ar), 131.34 (Ar), 131.77, 131.86 (C3'), 134.00 (Ar), 136.48 (C2'), 137.05 (C8), 150.20, 150.28 (C6), 155.88 (C2), 160.78, 160.86 (C4), 174.28, 174.39, 174.55, 174.65 (CO).

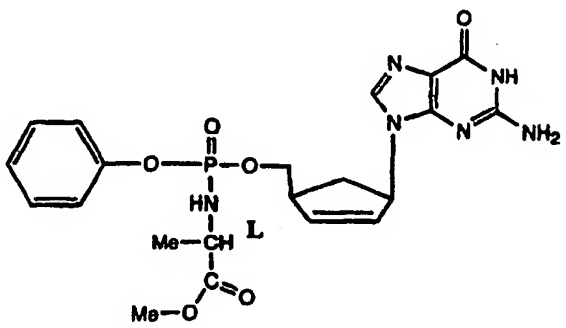
Example A

(1R, 4S)-9-[4-(hydroxymethyl)-2-cyclopenten-2-yl] guanine-5'-[phenyl-(methoxy-L-alaninyl)]-phosphate.

$C_{21}H_{25}O_6N_6P_1$, MW=488.45.

[0272] R. Vince and M. Hua, J. Med. Chem. 1990, 33, 17-21 describes a procedure for the sysnthesis of (1R,4S)-9-[4-(hydroxymethyl)-2-cyclopenten-1-yl] guanine. (1R,4S)-9-[4-(hydroxymethyl)-2-cyclopenten-1-yl] guanine (400mg, 1.618mmol) was dried by azeotroping with anhydrous pyridine (4x10ml), kept under N_2(g), and suspended in anhydrous THE (30ml). tBuMgCl (1.0M solution in THF) (1.6ml, 1.618mmol) was added dropwise and the resulting darker suspension vigorously stirred for 10mins. Phosphorochloridate (4.79ml, 2.43mmol) was added dropwise, and the reaction mixture stirred at room temperature for 69hrs. After this time, the suspended solid was partially in solution but a solid was still observed on the sides of the flask. More phosphorochloridate was added (4.79ml, 2.43mmol), and the reaction mixture stirred for a further 55hrs before being quenched by the addition of sat.NH_4Cl solution (0.25m). After stirring for a further 10mins, the solvent was removed under reduced pressure to give the crude product as a yellow gum which was solubilised in MeOH, dried over $MgSO_4$ (s), filtered and the filtrate reduced to dryness. The residue was solubilised in MeOH, silica added, and then the solvent removed to give the product preabsorbed onto silica which was loaded onto a silica column and eluted with 8% MeOH in $CHCl_3$. The product was further purified by gradient elution from 5→9 MeOH in DCM on a biotage flash-40 column, and after evaporation of the appropriate fractions, the product was obtained as a white foam (70mg, 8.6%).

[0273] The compound had the formula



^{31}P NMR (MeOH-d_4): δ 5.18, 4.86 (1:1).

^{1}H NMR: δ 7.67 (1H), 7.37-7.30 (2H), 7.21-7.14 (3H), 6.17-6.10 (1H), 5.97-5.94 (1H), 5.53-5.48 (1H), 4.28-4.15 (2H), 4.00-3.87 (1H), 3.66 (3H), 3.18 (1H), 2.83-2.71 (1H), 1.82-1.66 (1H), 1.36-1.29 (3H).

^{13}C NMR: δ 174.4*, 158.5, 154.1, 151.7, 151.1*, 136.9*, 136.5, 130.7, 129.7, 125.0, 120.4*, 116.8, 68.9*, 59.8, 51.7, 50.5*, 46.0*, 34.2, 19.3*.

MS ES$^+$: m/z 488.86 (100%) $(M)^+$, 500.04 (12%)$(M+Na)^+$, 507.96 (25%)$(M+K)^+$.

MS FAB: calculated m/z 489.165146, found m/z 489.164677.

***In vitro* Testing**

[0274] Cells were infected with HIV-1 as previously described [Balzarini *et al.* AIDS (1991), 5, 21-28]. Briefly, 5 x 10^5 cells per milliliter were infected with HIV-1 or HIV-2 at 100 $CCID_{50}$ (50% cell culture infective dose) per milliliter of cell suspension. Then 100 µL of the infected cell suspension was transferred to microtiter plate wells and mixed with 100 µL of the appropriate dilutions of the test compounds. After 4 days giant cell formation was recorded microscopically in the HIV-infected cell cultures [CEM]. The 50% effective concentration (EC_{50}) and 50% cytoxic concentration (CC_{50}) were defined as the compound concentrations required to reduce by 50% the number of giant cells or viable cells in the virus-infected and mock-infected cell cultures, respectively.

[0275] In the following Tables data columns are, in order.

HIV1 CEM: EC_{50} in µM for inhibition of HIV-1 in CEM cells.

HTV1 CEM: EC_{50} in μM for inhibition of HIV-2 in CEM cells.
CC50 CEM: CC_{50} in μM for toxicity to CEM cells.

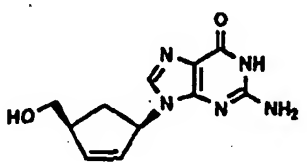
[0276] Table I below contains *in vitro* data comparing the biological activity of compound cf1490 with its non-phosphoramidated counterpart, Abacavir, and with the compound of comparative Example A and its non-phosphoramidated counterpart. Abacavir is currently used in the treatment of patients with HIV infection.

Table I

Compound	EC_{50}/μM HIV-1	EC_{50}/μM HIV-2	CC_{50}/μM	Fold Improvement
	CEM	CEM	CEM	
1490	0.07	0.09	13.1	30.2
Abacavir	1.9	3	78	
Example A	1.3	0.85	123	1.9
Nonphosphoramidated counterpart of Example A	2	2.3	157	

[0277] As can be seen in Table I compound cf 1490 embodying the present invention shows a much enhanced potency (27 to 33 fold) with respect to HIV *in vitro* than the known non-phosphoramidated Abacavir. The fold improvement in Table I is the mean increase in potency of the phosphoramidate compound versus its parent nucleoside for HIV 1 and HIV 2.

[0278] The surprising nature of this result is demonstrated having regard to Comparative Example A and its non-phosphoramidated counterpart. The structure of the non-phosphoramidated counterpart of Example A is *prima facie* similar to that of Abacavir. The phosphoramidate of Example A, however, shows a potency with respect to HIV which is merely comparable to that of its nonphosphoramidated counterpart, whose structural formula is:



[0279] Table II below compares the *in vitro* potency data of the compound 1490 with known equivalent data disclosed in PCT/GB96/00580 for known phosphoramidated compounds. The data in each case were obtained by the *in vitro* assay descibed above under "*In vitro* testing"

Table II

Compound	EC_{50}/μM HTV-1	EC_{50}/μM HIV-2	CC_{50}/μM
	CEM	CEM	CEM
1490	0.07	0.09	13.1
951	0.1	0.07	55
1078	0.55	0.65	209
1093	0.016	0.035	2.57

[0280] Each of compounds 951, 1078 and 1093 is a phosphoramidate of a nucleoside analogue.

[0281] Compound 951 is 2', 3'-dideoxy -2', 3'-didehydrothymidine 5'-(phenyl exthoxyalaninyl) phosphoramidate.

[0282] Compound 1078 is 2', 3'-dideoxy -2', 3'-didehydrothymidine 5'-(phenyl dimethoxyaspartyl) phosphoramidate.

[0283] Compound 1093 is 2', 3'-dideoxy adenosine 5'-(phenyl methoxyalaninyl) phosphoramidate.

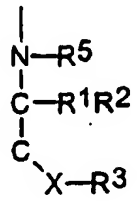
[0284] As can be seen from Table II the compound 1490 demonstrates a high degree of potency with respect to HIV.

[0285] Potency and toxicity data on an expanded range of compounds is presented in Table III, in which:

Cpd and Init refer to the compound reference numbers;

X refers to the aryl (phosphate) molety;

Y refers to the group;



Z refers to the bonding in the five membered sugar ring: = is unsaturated pentene;

H is saturated.

B in each case is "1592" which refers to the base present in Abacavir.

[0286] The data columns are, in order:

HTV 1 CEM: EC_{50} in μM for inhibition of HIV1 in CEM cells
HIV2 CEM: EC_{50} in μM for inhibition of HIV-2 in CEM cells
HIV2CEM.TK- EC_{50} μM for inhibition of HIV-2 in CEM/TK$^-$ cells
CC50 CEM: CC_{50} μM for toxicity to CEM cells
EC50 MSV: EC_{50} μM for inhibition of MSV
MCC MSV: minimum cytotoxic concentration in MSV essay.

Table III

Cpd	Init	X	Y	Z	B		HIV1 CEM	HIV2 CEM	HIV2 CEM TK-	CC50 CEM	EC50 MSV	MCC/MSV
1490	SH	PhO	MeAlaNH	=		1592	0.05	0.05		13.1	1.9	≥4
1640	SH	CH	AlaNH	=		1592	1.2	0.95		115		
1682	SH	PhO	BzAlaNH	=		1592	0.083	0.11	-	12.5		
1683	SH	PhO	Me-D-AlaNH	=		1592	1.38	4.5	-	64.3		
1684	SH	PhO	Me(Me2Gly)NH	=		1592	0.067	0.08	-	8.01		
1685	SH	PhO	MePheNH	=		1592	1.42	2.13	-	36.1		
1687	SH	PhO	EtAlaNH	=		1592	0.07	0.08	-	12.1		
1688	SH	PhO	Me3bNH	=		1592	1.78	2	-	≥100		
1689	SH	PhO	Me2AspNH	=		1592	1.42	1.9	-	44.2		
1695	SH	HO	D-AlaNH	=		1592	1.2	1.2	0.8	213		
1620	SH	p-ClPhO	MeAlaNH	=		1592	0.014	0.083	0.013	4.7		
1645	SH	PhO	iBuAlaNH	=		1592	3.7	6		33	11.7	≥20
1646	SH	PhO	PrAlaNH	=		1592	0.083	0.12		6	2	≥4
1647	SH	PhO	BuAlaNH	=		1592	0.066	0.17		6.23	0.82	≥4
1661	SH	PhO	iPrOAlaNh	=		1592	0.5	0.85		9.18	2.75	≥20
1971	AS	p-MeOCOC(OMe2)CPh	MeAlaNH	=		1592	0.1	0.12		12.1	9.2	≥20
1672	AS	PhO	iPrCH2AlaNH	=		1592	0.06	0.1		14.4	1.98	≥4
1673	AS	PhO	iBuCH2AlaNH	=		1592	0.15	0.18		8.07	2.92	≥4
1674	AS	PhO	iPrCH2CH2AlaNH	=		1592	0.25	0.25		10.7	2.04	≥4
1680	AHA	PhO	MeAlaNH	H		1592	12.5	17.5		237	≥100	≥100
1686	SS	PhO	3-pentyl Ala NH	=		1592	1.6	2	12.5	19.7	10.1	≥20
1690	SS	PhO	MeVal NH	=		1592	3.5	4	3.5	64.1	11.6	≥20
1687	SS	PhO	iBuCH2CH2AlaNH	=		1592	0.2	0.2	0.14	10.2	2.22	≥4
1702	AHA	-	-	H		1592	≥50	≥50		179	≥100	≥100
1706	SH	PhO	nPrAlaNH	=		1592	0.085	0.08		10.4	1.45	≥4
1707	SH	PhO	cHxAlaNH	=		1592	0.33	0.25		10.2	2.84	≥4
1708	SH	PhO	cHxCH2AlaNH	=		1592	0.15	0.18		15.1	1.3	≥4
1709	SH	PhO	Me(CHxCH2Gly)NH	=		1592	1.2	2		16	1.72	≥4
1710	SH	4-Br-PhO	MeAlaNH	=		1592	0.0055	0.049		5.78	0.61	≥0.8
1713	AS	4MeOC(MeO)2CCH2	MeAlaNH	=		1592	0.083	0.085		14	10.8	≥20
1714	AS	PhO	dIEtAsP	=		1592	0.55	2.1		23.1	7.18	≥20
1715	AS	PhO	MeMET	=		1592	1.16	2.73		48.0	10.2	≥20
1716	SS	PhO	MeLeuNH	=		1592	0.85	1.48		22	8.84	≥20
1719	SS	PhO	MeProN	=		1592	4	5.5		19.4	11.6	≥100
1720	SS	PhO	Bn2AspNH	=		1592						
1721	SS	PhO	IPr(CH2)3AlaNH	=		1592	0.05	0.14		12.5	2.2	≥4
1722	SS	PhO	cPentCH2AlaNH	=		1592	0.13	0.48		16.2		
1737	SH	p-F-PhO	MeAlaNH	=		1592						
1738	SH	p-I-PhO	MeAlaNH	=		1592						
1739	SH	PhO	nHxAlaNH	=		1592						
1740	AS	PhO	Me3GluNH	=		1592	3.5	5.33		36.9		
1741	AS	PhO	MeTrpNH	=		1592	3	3.67		18.3		
1742	AS	PhO	MePheNH	=		1592	7	5.33		24.2		
1743	AS	PhO	cHeptAlaNH	=		1592	1.3	1.05		6.32		

Acid stability

[0287] Compounds were tested for their stability towards acid-mediated hydrolytic decomposition employing a test designed to simulate stomach conditions. Each compound was incubated in dilute HCl of pH1 for 24 hours at 25°C. 0.3mg of compound were added to 1mL of 0.1N HCl at 25°C. HPLC was run immediately for time = 0 and at intervals up to approximately 24 hours.

[0288] The results for compound 1587, and for comparative compounds labelled 1001 and 1093 and described in PCT/GB96/00580, are given in table IV below.

Table IV

Compound	Time (hr)	Compound left (%)
1587	0	100
	22	77
1001	0	0
	17	0
1093	0	100
	13	0

[0289] Compound 1001 disappeared immediately (<1min). Compound 1093 degraded after less than 13 hours. The majority of compound 1587 remained in tact after 22 hours.

[0290] Each of compounds 1001 and 1093 is a phosporamidate of an adenosine analogue. Compound 1001 is 2', 3' -dideoxy -2',3' didehydroadenosine-5'- (phenylmethoxyalaninyl) phosphate. Compound 1093 is 2'3' -dideoxy adenosine 5'-(phenyl methoxyalaninyl) phosphate.

[0291] The results given in Table V above demonstrate the acid stability of a compound embodying the present invention compared to known compounds.

Biological stability

[0292] Compound 1587 of the present invention and the two comparative compounds 1001 and 1093 identified above were tested for their stability towards biological decomposition. Each compound was incubated in normal heparinised human plasma at 37°C for 4 hours. At selected time points (0, 15, 30 min, and 1, 2, 4 hours) duplicate samples were removed and deproteinated by acetonitrile extraction. Drug concentrations were then determined by LC/MS/MS analysis using standard methods. The results are shown in Table V below.

Table V

Compound	% Remaining at 4 hours	Half-life (hours)
1587	91	26
1001	52	4.6
1093	50	4.2

[0293] Under the conditions of the test the data in Table V shows a 6-fold stability advantage of compound 1587 over each of compounds 1001 and 1093.

Example 1

(1S,4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl ethoxy-L-alaninyl) phosphate Succinate Salt

(a) Phenylethoxy-L-alaninyl phosphorochloridate

[0294] L-alanine ethyl ester hydrochloride (3.0 g, 0.02 moles) was suspended in dry methylene chloride (40 mL). To this suspension was added phenyl phosphorodichloridate (2.9 mL, 0.02 mol) and the mixture was cooled to - 80 °C. N,N-Diisopropylethylamine (Aldrich, 6.8 mL, 0.04 mol) was added to the reaction in aliquots (1-2 mL) over a 1 h time

period. Reaction allowed to warm slowly to room temperature while stirring for 2 h. Organic solvent was removed in vacuo and the residue treated with diethyl ether (100 mL). The diethyl ether solution was filtered to remove insoluble inorganics and concentrated in vacuo to give the product as a colourless syrup. This product was used without further purification in part b.

(b) (1S,4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl ethoxy-L-alaninyl) nhosphate

[0295] (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol (1.5 g, 5.2 mmol) was dried by addition of dioxane and concentration in vacuo. To the dried nucleoside was added anhydrous pyridine (10 mL) and tetrahydrofuran (20 mL). Subsequently, tert-butyl magnesium chloride (6 mL, 1M solution in tetrahydrofuran, 6 mmol) was added slowly. The reaction was stirred for 20 min and a solution of phenyl ethoxy-L-alaninyl phosphorochloridate (part a, 3 g, 0.01 mol in 20 mL tetrahydrofuran) was added. The reaction was stirred at room temperature for 10 h and subsequently concentrated in vacuo to a brown syrup. This syrup was dissolved in methylene chloride (100 mL) the methylene chloride extracted with water (2x100 mL), dried ($MgSO_4$), filtered and concentrated to a brown solid foam. This solid foam was purified by flash chromatography using 5% methanol in chloroform as eluent to give 1.7 g (60 %) of, after purification, a 4:6 mixture of the phosphate isomers as a white solid foam. ^{1}H-NMR ($CDCl_3$): δ 7.47 (2 x s, 1H), 7.10-7.46 (m, 5H), 6.07 (m, 1H), 5.9 (m, 1H), 5.78 (s, 1H), 5.5 (m, 1H), 4.84 (bs, 2H), 4.1 (m, 4H), 4.00 (m, 1H), 3.64 (m, 1H), 3.14 (m, 1H), 3.0 (m, 1H), 2.78 (m, 1H), 1.68 (m, 1H), 1.36 (2xd, 3H), 1.22 (2xt, 3H), 0.86 (m, 2H), 0.6 (m, 2H); ^{31}P-NMR ($CDCl_3$): δ 3.05, 3.02.

Anal. Calcd. for $C_{25}H_{32}N_7O_5P$ x 1/4 $CHCl_3$: C, 53.07; H, 5.70; N, 17.15. Found: C, 52.81; H, 5.95; N, 16.91.

(c) (1S,4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl ethoxy-L-alaninyl) phosphate Succinate Salt

[0296] (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl ethoxy-L-alaninyl)phosphate (part 1b, 376 mg, 0.7 mmol) was dissolved in ethanol. To this solution was added succinic acid (82 mg, 0.7 mmol) and the resulting solution evaporated to dryness. The residue was dissolved in acetonitrile (10-20 mL) with heating. Precipitate formed upon cooling. The mixture was stored in the refrigerator overnight and solid collected by filtration to give 330 mg (72 %) of a 4:6 mixture of the phosphate isomers as a solid; ^{1}H-NMR (DMSO-d_6): δ 12.14 (s, 2H), 7.58 (s, 1H), 7.1-7.4 (m, 6H), 5.9-6.1 (m, 3H), 5.85 (broad s, 2H), 5.42 (m, 1H), 3.95-4.15 (m, 4H), 3.8 (m, 1H), 3.05 (m, 2H), 2.65 (m, 1H), 2.4 (s, 4H), 1.63 (m, 1H), 1.4 (2xd, 3H), 1.12 (t, 3H), 0.5-0.7 (m, 4H); ^{31}P-NMR (DMSO-d_6): δ; 4.00 and 3.68; high resolution mass spectrum: calcd for $C_{25}H_{32}N_7O_5P$ (M+H)$^+$ (m/z) 542.2281, found 542.2282.

Anal. Calcd. for $C_{25}H_{32}N_7O_5P{\cdot}C_4H_6O_4{\cdot}1/2H_2O$: C, 52.09; H, 5.87; N, 14.66. Found: C, 52.13; H, 5.72; N, 14.61.

Example 2

(1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl methoxy-L-alaninyl)phosphate Succinate Salt

(a) Phenylmethoxy-L-alaninyl phosphorochloridate.

[0297] L-alanine methyl ester hydrochloride (10 g, 0.072 mol) was suspended in dry methylene chloride (100 mL). To this suspension was added phenyl phosphorodichloridate (10.7 g, 7.6 mL) and the mixture was cooled to -80 °C. Subsequently N,N-Diisopropylethylamine (Aldrich, 25 mL) was added to the reaction in aliquots (1-2 mL) over a 1 h time period. The solution was stirred for 30 min at -80°C, then allowed to warm slowly to room temperature while stirring for 2 h. Organic solvent was removed in vacuo and the residue treated with diethyl ether (100 mL). The diethyl ether solution was filtered to remove insoluble inorganics and concentrated in vacuo to give the product as a colorless syrup: ^{31}P-NMR ($CDCl_3$) δ 8.61; 8.37 ppm. This product was used without further purification in Example 2b

(b) (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl methoxy-L-alaninyl)phosphate

[0298] (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol (5.5 g, 0.018 moles) was dried by addition of dioxane and concentration in vacuo. To the dried nucleoside was added anhydrous tetrahydrofuran (30 mL) and pyridine (40 mL). Subsequently tert-butyl magnesium chloride (23 mL, 1M solution in tetrahydrofuran, 1.3 equivalents) was added slowly. The reaction was stirred for 20 min and a solution of phenylmethoxy-L-alaninyl phosphorochloridate (12 g, 0.043 moles, 2.5 equivalents in 20 mL THE) was added. The reaction was stirred

at room temperature for 12 h and subsequently concentrated in vacuo to a brown syrup. This syrup was dissolved in methylene chloride (100 mL) the methylene chloride extracted with water (2x100 mL), dried ($MgSO_4$), filtered and concentrated to a brown foam. This foam was purified by flash chromatography using 5% methanol in chloroform as eluent to give 6.9 g (75 %) of a mixture of the phosphate isomers of the title compound as a white solid foam. ^{1}H-NMR ($CDCl_3$): δ 7.5 (2 x s, 1H), 7.1-7.4 (m, 5H), 6.1 (m, 1H), 5.9 (m, 2H), 5.5-5.6 (m, 1H), 4.9 (bs, 2H), 4.2 (m, 2H), 4.05 (m, 1H), 3.7 (s, 3H), 3.6-3.8 (m, 1H) 3.17 (m, 1H), 3.0 (m, 1H), 2.8 (m, 1H), 1.7 (m, 1H), 1.4 (2 x d, 3H), 0.9 (m, 2H), 0.6 (m, 2H); ^{31}P-NMR (CDC13): δ 3.07, 3.02.

Anal. Calcd. for $C_{24}H_{30}N_7O_5P$ x 2/5 $CHCl_3$: C, 50.94; H, 5.33; N, 17.00. Found: C, 50.83; H, 5.39; N, 16.94.

(c) (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl methoxy-L-alaninyl)phosphate Succinate Salt

[0299] (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl methoxy-L-alaninyl)phosphate (part b, 100 mg, 0.19 mmol) was dissolved in methanol. To this solution was added succinic acid (22 mg, 0.19 mmol) and the resulting solution evaporated to dryness. The residue was dissolved in acetonitrile (10mL) with heating. Precipitate formed upon cooling. The mixture was stored in the refrigerator overnight and solid collected by filtration to give 70 mg (57%) of a mixture of the phosphate isomers as a solid; ^{1}H-NMR (DMSO-d_6): δ 12.15 (s, 2H, D_2O exchangeable), 7.61 (s, 1H), 7.36 (3H, becomes 2H on D_2O exchange), 7.20 (3H), 5.9-6.1 (m, 3H), 5.88 (broad s, 2H, D_2O exchangeable), 5.44 (m, 1H), 4.0-4.2 (m, 2H), 3.85 (m, 1H), 3.60 (s, 3H), 3.05 (2H), 2.65 (m, 1H), 2.44 (s, 4H), 1.64 (m, 1H), 1.23 (m, 3H), 0.5-0.7 (m, 4H); ^{31}P-NMR (DMSO-d_6): δ; 3.99 and 3.66;
Anal. Calcd. for $C_{24}H_{30}N_7O_5P{\cdot}C_4H_6O_4{\cdot}1/2H_2O$: C, 51.38; H, 5.70; N, 14.98. Found: C, 51.36; H, 5.66; N, 14.99.

Example 3

(1S,4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl ethoxy-L-alaninyl) phosphate Fumarate Salt

[0300] (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl ethoxy-L-alaninyl)phosphate (198 mg, 0.37 mmol) was dissolved in ethanol. To this solution was added fumaric acid (43 mg, 0.37 mmol) and the resulting solution evaporated to dryness. The residue was dissolved in acetonitrile (10 mL) with heating. Precipitate formed upon cooling. The mixture was stored in the refrigerator overnight and solid collected by filtration to give 185 mg (75 %) of a 4:6 mixture of the phosphate isomers as a solid; ^{1}H-NMR (DMSO-d_6): δ 7.6 (s, 1H), 7.1-7.4 (m, 6H), 6.64 (s, 2H), 5.9-6.1 (m, 3H), 5.87 (broad s, 2H), 5.44 (m, 1H), 3.95-4.15 (m, 4H), 3.84 (m, 1H), 3.05 (m, 2H), 2.65 (m, 1H), 1.63 (m, 1H), 1.23 (m, 3H), 1.15 (t, 3H), 0.5-0.7 (m, 4H); ^{31}P-NMR (DMSO-d_6): δ; 4.00 and 3.67.

Anal. Calcd. for $C_{25}H_{32}N_7O_5P{\cdot}C_4H_4O_4{\cdot}1/2H_2O$: C, 52.25; H, 5.59; N, 14.71. Found: C, 52.25; H, 5.51; N, 14.49.

Example 4

(1S,4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl ethoxy-L-alaninyl) phosphate Glutarate Salt

[0301] (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl ethoxy-L-alaninyl)phosphate (part 1b, 200 mg, 0.38 mmol) was dissolved in ethanol. To this solution was added glutaric acid (50 mg, 0.38 mmol) and the resulting solution evaporated to dryness. The residue was dissolved in acetonitrile (10 mL) with heating. The mixture was stored in the refrigerator overnight and solid collected by filtration to give 130 mg (50 %) of a 67:33 mixture of the phosphate isomers as a solid; ^{1}H-NMR (DMSO-d_6): δ 7.6 (s, 1H), 7.1-7.4 (m, 6H), 5.9-6.1 (m, 3H), 5.87 (broad s, 2H), 5.44 (m, 1H), 3.95-4.2 (m, 4H), 3.8 (m, 1H), 3.1 (m, 2H), 2.65 (m, 1H), 2.25 (t, 4H), 1.7 (m, 3H), 1.23 (m, 3H), 1.15 (t, 3H), 0.5-0.7 (m, 4H); ^{31}P-NMR (DMSO-d_6): δ; 4.00 and 3.68.

Anal. Calcd. for $C_{25}H_{32}N_7O_5P$ $C_5H_8O_4$1/2H_2O: C, 52.78; H, 6.05; N, 14.36. Found: C, 52.97; H, 6.07; N, 14.33.

Example 5

(1S,4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(pheny) ethoxy-L-alaninyl) phosphate D-Tartrate Salt

[0302] (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl ethoxy-L-alaninyl)phosphate (157 mg, 0.29 mmol) was dissolved in ethanol. To this solution was added D-tartaric acid (44 mg,

0.29 mmol) and the resulting solution evaporated to dryness. The residue was dissolved in acetonitrile (10 mL) with heating. The mixture was stored in the refrigerator overnight and solid collected by filtration to give 112 mg of a 53:47 mixture of the phosphate isomers as a solid; ^{1}H-NMR (DMSO-d_6): δ 7.6 (s, 1H), 7.1-7.4 (m, 6H), 5.8-6.2 (m, 5H), 5.44 (m, 1H), 4.3 (s, 2H), 3.95-4.2 (m, 4H), 3.8 (m, 1H), 3.35 (broad s, 2H), 3.1 (m, 2H), 2.65 (m, 1H), 1.7 (m, 1H), 1.23 (m, 3H), 1.15 (t, 3H), 0.5-0.7 (m, 4H);^{31}P-NMR (DMSO-d_6): δ; 4.00 and 3.67.

Example 6

(1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl methoxy-L-alaninyl)phosphate Diastereomers

[0303] An approximately 1:1 mixture of diastereomers of (1S,4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl methoxy-L-alaninyl)phosphate was prepared using similar methodology as above: ^{1}H-NMR ($CDCl_3$): δ 7.5 (2 x s, 1H), 7.1-7.4 (m, 5H), 6.1 (m, 1H), 5.9 (m, 2H), 5.5-5.6 (m, 1H), 4.9 (bs, 2H), 4.2 (m, 2H), 4.05 (m, 1H), 3.7 (s, 3H), 3.6-3.8 (m, 1H) 3.17 (m, 1H), 3.0 (m, 1H), 2.8 (m, 1H), 1.7 (m, 1H), 1.4 (2 x d, 3H), 0.9 (m, 2H), 0.6 (m, 2H); ^{31}P-NMR ($CDCl_3$): δ 3.07, 3.02.

Anal. Calcd. for $C_{24}H_{30}N_7O_5P$ x 2/5 $CHCl_3$: C, 50.94; H, 5.33; N, 17.00. Found: C, 50.83; H, 5.39; N, 16.94.

[0304] The phosphate isomers were separated with Supercritical Fluid Chromatography using a Chiralpak AS (product name) column, 25 % methanol in carbon dioxide as the eluent, flow rate 2 mL/min, temperature 40°C, and pressure 2.068428x10^7 Pa (3000psi). The first isomer to elute had a RT of 2.9 min and was 100% enantiopure; evaporation of solvents gave the isomer as a white solid foam: ^{1}H-NMR ($CDCl_3$): δ 7.50 (s, 1H), 7.3-7.4 (m, 2H), 7.15-7.25 (m, 3H), 6.11 (m, 1H), 5.91 (m, 1H), 5.86 (s, 1H), 5.55 (m, 1H), 4.89 (s, 2H), 4.24 (m, 2H), 4.05 (m, 1H), 3.72 (s, 3H), 3.65 (m, 1H), 3.20 (m, 1H), 3.02 (m, 1H), 2.83 (m, 1H), 1.72 (m, 1H), 1.37 (d, 3H), 0.89 (m, 2H), 0.62 (m, 2H); ^{31}P-NMR ($CDCl_3$): δ 3.07.

Anal. Calcd. for $C_{24}H_{30}N_7O_5P$ x 1/7 $CHCl_3$: C, 53.25; H, 5.58; N, 18.00. Found: C, 53.27; H, 5.69; N, 17.72.

[0305] The second isomer to elute had a RT of 6.7 min and was 100% enantiopure; evaporation of solvents gave the isomer as a white solid foam: ^{1}H-NMR ($CDCl_3$): δ 7.52 (s, 1H), 7.25-7.4 (m, 2H), 7.15-7.22 (m, 3H), 6.11 (m, 1H), 5.94 (m, 1H), 5.85 (s, 1H), 5.55 (m, 1H), 4.88 (s, 2H), 4.22 (m, 2H), 4.04 (m, 1H), 3.75 (s, 3H), 3.7-3.75 (m, 1H), 3.17 (m, 1H), 3.04 (m, 1H), 2.80 (m, 1H), 1.73 (m, 1H), 1.42 (d, 3H), 0.89 (m, 2H), 0.67 (m, 2H); ^{31}P-NMR ($CDCl_3$): δ 3.0.

Anal. Calcd. for $C_{24}H_{30}N_7O_5P$ x 1/5 $CHCl_3$: C, 52.71; H, 5.52; N, 17.78. Found: C, 52.61; H, 5.67; N, 17.53.

Example 7

(1S,4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl N-methylamino-L-alaninyl) phosphate Sodium Salt

[0306] (1S,4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl methoxy-L-alaninyl)phosphate (0.060 g, 0.11 mmoles) was suspended in solution of 40% aqueous methylamine (60 ml) and stirred at room temperature for 18 hours. The volatiles were removed by spin evaporation *in vacuo* and the residue was dissolved in water (50 ml), extracted with dichloromethane (2x50 ml) and purified by anion exchange chromatography on a Sep-Pak® Vac 35cc Accell™ Plus QMA cartridge (Waters Corp., P/N WAT054725) (HCO_3^- form) with an aqueous ammonium bicarbonate buffer (0 - 0.5 M gradient, 1 L). The appropriate fractions were combined and the volatiles were remove by spin evaporation *in vacuo*. The residue was twice dissolved in deionized water and spin evaporated *in vacuo* to give (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl N-methylamino-L-alaninyl) phosphate as the ammonium salt. This salt was dissolved in deionized water and passed through a Sep-Pak® Vac 20cc Accell™ Plus CM cartridge (Waters Corp., P/N WAT054675) (Na^+ form) using deionized water. The appropriate fractions were combined and lyophilized to give 0.026 g (46% yield) of (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purr-9-yl)-2-cyclopentene-1-methanol O-(phenyl N-methylamino-L-alaninyl) phosphate sodium salt 2.2 hydrate as a white solid:: MS (ES^-) *m/e* 449 (MH^-).

Anal. Calcd. for $C_{18}H_{26}N_8NaO_4P \cdot 2.2\ H_2O$: C, 42.22; H, 5.98; N, 21.88. Found: C, 42.36; H, 5.77; N, 21.66.

Example 8

(1S,4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl N-cyclopropylamino-L-alaninyl) phosphate Sodium Salt

[0307] (1S,4R)4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl N-cyclopropylamino-L-alaninyl) phosphate sodium salt was prepared by a method analogous to that used to prepare (1S,4R)-

4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl N-methylamino-L-alaninyl) phosphate sodium salt except that the 40% aqueous methylamine solution was replaced by a solution of cyclopropylamine (5 ml, 72 mmoles) in deionized water (50 ml). Lyophilization of the combined fractions gave 35 mg (58% yield) of (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl N-cyclopropylamino-L-alaninyl) phosphate sodium salt 2.5 hydrate as a white solid: MS (ES^-) *m/e* 475 (MH^-).

Anal. Calcd. for $C_{20}H_{28}N_8NaO_4P \cdot 2.5\ H_2O$: C, 44.20; H, 6.12; N, 20.61. Found: C, 44.27; H, 5.81; N, 20.49.

Example 9

(1S,4R)-4-(2-Amino-6-cyclopropylamin-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl N,N-dimethylamino-L-alaninyl) phosphate Sodium Salt

[0308] (1S,4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl N-dimethylamino-L-alaninyl) phosphate sodium salt was prepared by a method analogous to that used to prepare (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl N-methylamino-L-alaninyl) phosphate sodium salt except that the 40% aqueous methylamine solution was replaced by a 40% aqueous dimethylamine solution (50 ml). Lyophilization of the combined fractions gave 39 mg (59% yield) of (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl N,N-dimethylamino-L-alaninyl) phosphate sodium salt trihydrate as a white solid: MS (ES^-) *m/e* 463 (MH^-).

Anal. Calcd. for $C_{19}H_{28}N_8NaO_4P \cdot 3.0\ H_2O$: C, 42.22; H, 6.34; N, 20.73. Found: C, 42.40; H, 6.01; N, 20.51

Example 10

(1S,4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(L-alaninyl) phosphate Disodium Salt

[0309] (1S,4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl methoxy-L-alaninyl)phosphate (0.5 g, 0.95 mmoles) was suspended in solution of triethylamine (30 ml) and deionized water (30 ml) and stirred at room temperature for 18 hours. The volatiles were removed by spin evaporation *in vacuo* and the residue was dissolved in water (50 ml), extracted with dichloromethane (2x50 ml) and purified by anion exchange chromatography on a Sep-Pak® Vac 35cc Accell™ Plus QMA cartridge (Waters Corp., P/N WAT054725) (HCO_3^- form) with an aqueous ammonium bicarbonate buffer (0 - 0.5 M gradient, 1 L). The appropriate fractions were combined and the volatiles were remove by spin evaporation *in vacuo*. The residue was twice dissolved in deionized water and spin evaporated *in vacuo* to give (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(L-alaninyl) phosphate as the ammonium salt. This salt was dissolved in deionized water and passed through a Sep-Pak® Vac 20cc Accell™ Plus CM cartridge (Waters Corp., P/N WAT054675) (Na^+ form) using deionized water. The appropriate fractions were combined and lyophilized to give 0.430 g (86% yield) of (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(L-alaninyl) phosphate disodium salt 2.5 hydrate as a white solid: MS (ES^-) *m/e* 436 (MH^-).

Anal. Calcd. for $C_{17}H_{22}N_7Na_2O_5P \cdot 2.5\ H_2O$: C, 38.79; H, 5.17; N, 18.63. Found: C, 38.62; H, 5.11; N, 18.43.

Anti-Hepatitis B Virus Activity

[0310] Compounds of Example 1 to 10 were tested for anti- Hepatitis B Virus activity according to the method described by Jansen, R. et al., *Antimicrobial Agents and Chemotherapy*, Vol. 37, No. 3, pp. 441-447, 1993. Representative IC_{50} values were in the range of 0.017μM - 3.0 μM.

The solubility and solution/solid state stability of three salt forms of (1S, 4R)-4-[2-amino-6-(cyclopropylamino)-9(H)-purin-9-yl]-2-cyclopentene-1-methanol O-(phenyl ethoxy-L-alaninyl) phosphate

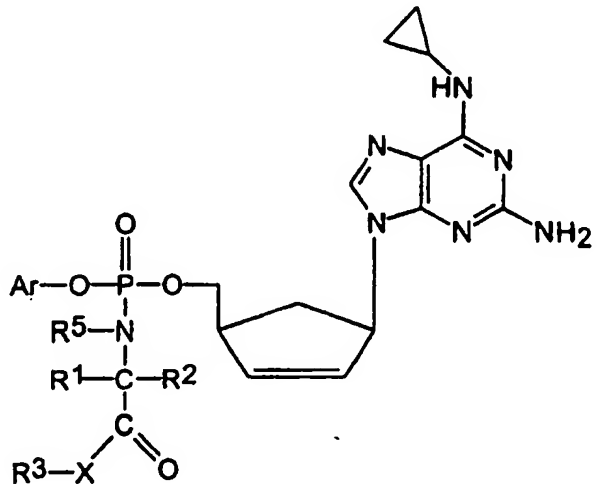
[0311] The salts have handling and formulation advantages in that they are stable, free-flowing crystalline solids that do not change composition, even at elevated temperature and humidity. The free base of (1S, 4R)-4-[2-amino-6-(cyclopropylamino)-9(H)-purin-9-yl]-2-cyclopentene-1-methanol O- (phenyl ethoxy-L-alaninyl) phosphate in contrast, is a hygroscopic, amorphous solid foam that could not be crystallized.

Form	Solid Type*	0.1 N HCl		PBS		HPMC/Tween		Solid State Stability (%)
		Solubility (mg/mL)	Stability (%)	Solubility (mg/mL)	Stability (%)	Solubility (mg/mL)	Stability (%)	
Free Base	Amorphous Hygroscopic	> 5	69.1	0.054	98.5	0.04	97.6	93.7
Glutarate	crystals	>5	69.3	0.084	99.9	>0.25, <1	98.6	98.9
Fumarate	crystals	>5	70.0	0.086	98.5	0.22	983	97.1
Succinate	crystals	>5	66.0	0.069	99.8	>0.25, <1	98.8	99.6
Solution stability = % of parent (AUC) after 27 hr at room temperature, normalized to initial AUC. Solid state stability = % of parent (AUC) after two weeks at 60°C, normalized to initial AUC.								

[0312] The free bases of the phosphoramidates of 2',3'-dideoxy adenosine and 2',3'-dideoxy-2',3'-didehydroadenosine are hygroscopic amorphous foams or gums. However, their instability to acid prevents advantageous utilization of complexes with acids to form salts with improved physical properties; exposure to acids degrades these compounds rapidly. (1S, 4R)-4-[2-amino-6-(cyclopropylamino)-9(H)-purin-9-yl]-2-cyclopentene-1-methanol (abacavir) has enhanced stability to acid, compared to nucleosides containing labile glycosidic bonds between heterocycle and sugar. Thus phosphoramidate protides of abacavir form stable salts that have been found to have advantageous physical properties suitable for pharmaceutical development.

Claims

1. A compound of the formula (I):



wherein

Ar is an aryl group

R^1 and R^2 are each independently selected from the group comprising H, alkyl and aryl groups,

X is selected from the group comprising O, NH, NR^4 and S wherein R^4 is selected from the group comprising

alkyl and aryl;

R^5 is selected from the group comprising H, alkyl and aryl groups, wherein when R^1 and R^5 are each alkyl they may be linked to form a 5- or 6- membered ring;

and R^3 is selected from the group comprising H, alkyl, aryl, heterocyclic and polycyclic groups,

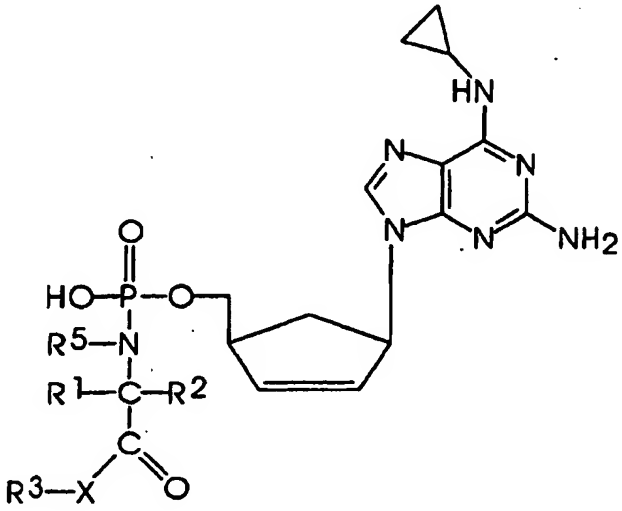
or a pharmaceutically acceptable derivative or metabolite thereof.

2. A compound according to claim 1 wherein

Ar is phenyl or substituted phenyl.

3. A compound according to any one of claims 1 to 2 wherein R^3 is selected from the group comprising $-CH_3$, $-C_2H_5$ and $-CH_2Ph$.

4. A compound of the formula (II):



wherein R^1, R^2, R^3, R^5 and X have the meanings ascribed in Claim 1.

5. A compound according to any one of claims 1 to 4 wherein R^1 and R^2 are the same or different and are H, $-CH_3$ or $-CH_2CH_3$.

6. A compound according to any one of claims 1 to 4 wherein R^1 is H and R^2 is $-CH_3$, $-CH_2CH_3$ or $-CH_2$-Ph.

7. A compound according to any one of claims 1 to 6 wherein the C atom bearing R^1 and R^2 is chiral.

8. A compound according to any one of claims 1 to 6 wherein the compound has L chirality with respect to the C atom bearing R^1 and R^2.

9. A compound according to any one of claims 1 to 8 wherein X is O.

10. A compound selected from:

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[L-alaninyl] phosphate diammonium salt

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl benzyloxy-L-

alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy-D-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy-α, α-dimethylglycinyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy-L-phenylalaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl ethoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxyglycinyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl L-aspartyl dimethyl ester] phosphate.

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[4-chlorophenyl methoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl tertbutyloxy-L-alaninyl] phosphate

(1 S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[Phenyl n-propoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[Phenyl n-butyloxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[Phenyl i-propoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[(p-(2",2"-dimethoxy-propionic acid methyl ester) phenyl) methoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl (2-methylpropyl)oxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl (2,2-dimethylpropyl)oxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl 3-methylbutyloxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl 3-pentyloxy-L-alaninyl] phosphate

1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy-L-valinyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl 3,3-dimethyl-1-butyloxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[Phenyl n-pentyloxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[Phenyl cyclohexyloxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[Phenyl cyclohexanemethoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[Phenyl methoxy-3-cyclohexane-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[4-bromophenyl methoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl diethoxy-L-aspartyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy-L-methionyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy-L-leucinyl]phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy-L-prolinyl]phosphate.

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentene-1-methylene-[phenyl dibenzyloxy-L-aspartinyl]phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl 4-methyl-1-pentyloxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl cyclopentylmethoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[4-fluorophenyl methoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[4-iodophenyl methoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl dimethoxy-L-glutamyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy-L-tryptophanyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy-L-isoleucinyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl cycloheptanyloxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl cyclobutylmethoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl cyclopropylmethoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl cyclobuty-

loxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl cyclopentyloxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl phenethoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl 3-phenyl-1-propoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[phenyl 4-phenyl-1-butoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl 2-cyclohexyl-1-ethoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl 3-cyclohexyl-1-propoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl 4-cyclohexyl-1-butoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy-α-ethyl-L-glycinyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy-a-phenyl(RS)glycinyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy-a-propyl-L-glycinyl] phosphate)

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-([phenyl methoxy-α-butyl-RS-glycinyl]phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[p-phenoxyphenyl methoxy-L-alaninyl]phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[p-phenylphenyl methoxy-L-alaninyl)]phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[4-hydroxyacetophenone methoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[4-butylphenyl methoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[p-methoxyphenyl methoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[p-propoxyphenyl methoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy-α, α-cyclopentylglycinyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy-α, α-cylohexylglycinyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[phenyl methoxy-α, α-cylopropylglycinyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[p-(methoxycarbonyl)phenyl methoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl)-2-cyclopentene-1-methanol O-[p-(trifluoromethylthio)phenyl methoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[p-(2-methoxyvinyl) phenyl methoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanolO-[p-(2-phenylcarbonyl-vinyl)phenyl methoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[p-(2,2-dicyanovinyl) phenyl methoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol O-[o-(carboxylate ethyl ester)phenyl methoxy-L-alaninyl] phosphate

(1S,4R)-4-(2-ammo-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl ethoxy-L-alaninyl) phosphate succinate salt

(1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9yl)-2-cyclopentene-1-methanol O-(phenyl methoxy-L-alaninyl) phosphate succinate salt

(1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl ethoxy-L-alaninyl) phosphate fumarate salt

(1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl ethoxy-L-alaninyl) phophate glutarate salt

(1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl ethoxy-L-alaninyl) phosphate D-tartrate salt

(1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl methoxy-L-alaninyl) phophate diastereoisomers

(1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl N-methyl-amino-L-alaninyl) phosphate sodium salt

(1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl N-cyclopropylamino-L-alaninyl) phosphate sodium salt

(1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(phenyl N,N-dimethylamino-L-alaninyl) phosphate sodium salt

(1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentene-1-methanol O-(L-alaninyl) phosphate disodium salt.

11. Use of a compound according to any one of claims 1 to 3, to claim 10, or to any one of claims 5 to 9 as dependent on any one of claims 1 to 3 in the manufacture of a medicament for the treatment or prophylaxis of a viral infection.

12. Use of a compound according to claim 11 wherein the viral infection comprises HIV.

13. Use of a compound according to claim 11 wherein the viral infection comprises HBV.

14. A compound according to any one of claims 1 to 3, to claim 10, or to any one of claims 5 to 9 as dependent on any one of claims 1 to 3 for use in a method of treatment, prophylaxis or diagnosis.

15. A compound according to claim 14 wherein the method comprises a method of prophylaxis or treatment of viral infection comprising administration to a patient in need of such treatment an effective dose of the compound.

16. A compound according to claim 15 wherein the viral infection is HIV.

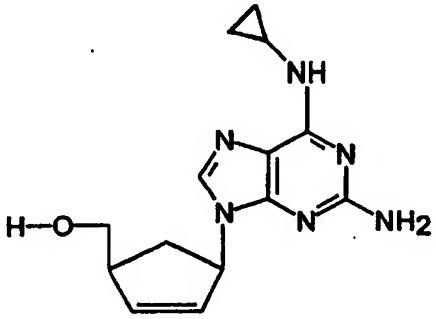
17. A compound according to claim 15 wherein the viral infection is HBV.

18. A compound according to any one of claims 14 to 17 wherein the method comprises administering orally to a patient an effective dose of the compound.

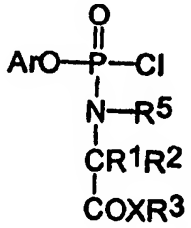
19. A pharmaceutical composition comprising a compound according to any one of claims 1 to 3, to claim 10, or to any one of claims 5 to 9 as dependent on any one of claims 1 to 3 in combination with a pharmaceutically acceptable excipient.

20. A composition according to claim 19 in a form for oral administration.

21. A process for the preparation of a compound according to any one of claims 1 to 3, to claim 10, or to any one of claims 5 to 9 as dependent on any one of claims 1 to 3 comprising reacting a compound having the formula

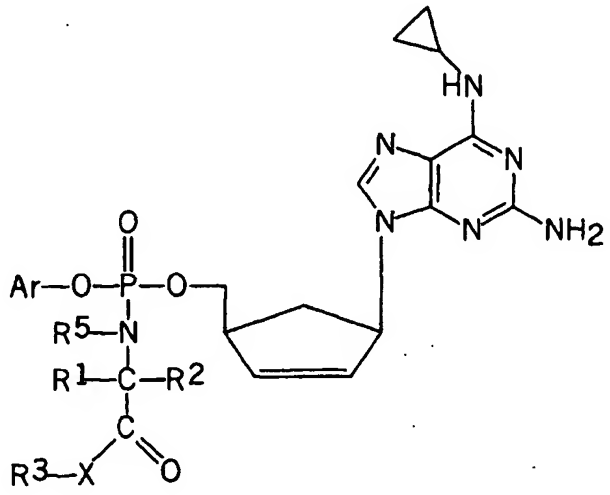


with a compound of formula



Revendications

1. Un composé de formule (I):



où

Ar est un groupement aryle

R^1 et R^2 sont chacun sélectionnés indépendamment parmi le groupe composé de H, de groupements alkyle et aryle,

X est sélectionné à partir du groupe composé de O, NH, NR^4 et S où R^4 est sélectionné parmi le groupe comprenant les alkyle et aryle ;

R^5 est sélectionné parmi le groupe composé de H, de groupements alkyle et aryle, où lorsque R^1 et R^5 sont chacun alkyle ils peuvent être reliés pour former un noyau à 5 ou 6 membres ;

et R^3 est sélectionné parmi le groupe comprenant les H, groupements alkyle et aryle hétérocycliques et polycycliques,

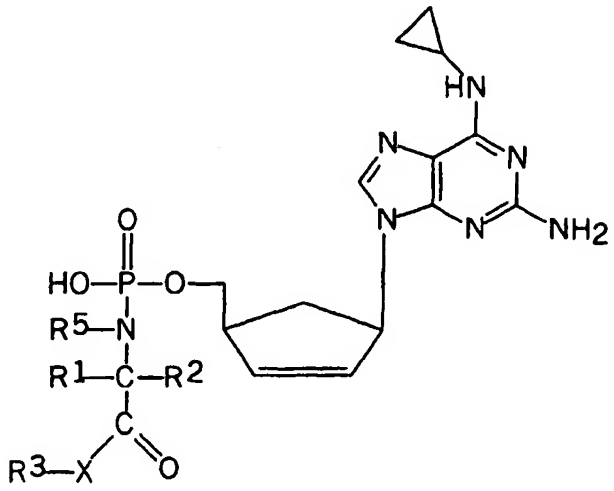
ou un dérivé ou métabolite pharmaceutiquement acceptable de celui-ci.

2. Un composé suivant la revendication 1 où

Ar est le phényle ou phényle substitué.

3. Un composé suivant n'importe laquelle des revendications 1 à 2 où R^3 est sélectionné parmi le groupe comprenant les-CH_3, -C_2H_5 et -CH_2Ph.

4. Un composé de formule (II):



où R^1, R^2, R^3, R^5 et X ont les significations décrites dans la Revendication 1.

5. Un composé suivant n'importe laquelle des revendications 1 à 4 où R^1 et R^2 sont identiques ou différents et sont H, $-CH_3$ ou $-CH_2CH_3$.

6. Un composé suivant n'importe laquelle des revendications 1 à 4 où R^1 est H et R^2 est $-CH_3$, $-CH_2CH_3$ ou $-CH_2$-Ph.

7. Un composé suivant n'importe laquelle des revendications 1 à 6 où l'atome C qui contient R^1 et R^2 est chiral.

8. Un composé suivant n'importe laquelle des revendications 1 à 6 où le composé a une chiralité L par rapport à l'atome C qui contient R^1 et R^2.

9. Un composé suivant n'importe laquelle des revendications 1 à 8 où X est O.

10. Un composé sélectionné parmi :

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl méthoxy-L-alaninyl] phosphate.

Sel de (1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[L-alaninyl] phosphate diammonium.

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl benzyloxy-L-alaninyl] phosphate.

(1S,4R)4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopertène-1-méthanol O-[phényl méthoxy-D-alaninyl] phosphate.

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl méthoxy-a,a-diméthylglycinyl] phosphate.

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl méthoxy-L-phénylalaninyl] phosphate.

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl éthoxy-L-alaninyl] phosphate.

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl méthoxyglycinyl] phosphate.

1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl L-aspartyl diméthyle ester] phosphate.

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[4-chlorophényl méthoxy-L-alaninyl] phosphate.

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl tertbutyloxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[Phényl n-propoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[Phényl n-butyloxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[Phényl i-propoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[(p-(2",2"-acide diméthoxypropionique méthyl ester) phényl) méthoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl (2-méthylpropyl)oxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl (2,2-diméthylpropyl)oxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl 3-méthylbutyloxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl 3-pentyloxy-L-alaninyl] phosphate

1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol-O-[phényl méthoxy-L-valinyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl 3,3-diméthyl-1-butyloxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[Phényl n-pentyloxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[Phényl cyclohexyloxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[Phényl cyclohexane-méthoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[Phényl méthoxy-3-cyclohexane-L-alaninyl] phosphate

1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[4-bromophényl méthoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl diéthoxy-L-as-

partyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl méthoxy-L-méthionyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl méthoxy-L-leucinyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl méthoxy-L-prolinyl] phosphate.

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl dibenzyloxy-L-aspartinyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl 4-méthyle-1-pentyloxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amio-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl cyclopentylméthoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[4-fluorophényl méthoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[4-iodophényl méthoxy-L-alaninyl] phosphate

(1S,4R)-4- [2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl diméthoxy-L-glutamyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl méthoxy-L-tryptophanyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl méthoxy-L-isoleucinyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl cycloheptanyloxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl cyclobutylméthoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl cyclopropylméthoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl cyclobutyloxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl cyclopentyloxy-L-alaninyl]phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl phénéthoxy-L-alaninyl]phosphate

(1S,4R)4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl 3-phényl-1-propoxy-L-alaninyl]phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl 4-phényl-1-butoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl 2-cyclohexyl-1-éthoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl 3-cyclohexyl-1-propoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl 4-cyclohexyl-1-butoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amio-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl méthoxy-a-éthyl-L-glycinyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl méthoxy-a-phényl(RS)glycinyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl méthoxy-a-propyl-L-glycinyl] phosphate)

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-([phényl méthoxy-a-butyl-RS-glycinyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[p-phénoxyphényl méthoxy-L-alaninyl]phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[p-phénylphényl méthoxy-L-alaninyl)]phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[4-hydroxyacetophénone méthoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[4-butylphényl méthoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[p-méthoxyphényl méthoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[p-propoxyphényl méthoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl)-2-cyclopentène-1-méthanol O-[phényl méthoxy-α,α-cyclopentylglycinyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl méthoxy-α,α-cylohexylglycinyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[phényl méthoxy-a,a-cylopropylglycinyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol 1 O-[p-(méthoxycarbonyl)phényl méthoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[p-(trifluorométhylthio) phényl méthoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[p-(2-méthoxyvinyl) phényl méthoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[p-(2-phénylcarbonylvi-

nyl)phényl méthoxy-L-alaninyl] phosphate

(1S,4R)-4-[2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[p-(2,2-dicyanovinyl) phényl méthoxy-L-alaninyl] phosphate

(1S,4R)-4- [2-amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopentène-1-méthanol O-[o-(carboxylate éthyl ester)phényl méthoxy-L-alaninyl] phosphate

Sel succinate de (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentène-1-méthanol O-(phényl éthoxy-L-alaninyl) phosphate

Sel succinate de (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9yl)-2-cyclopentène-1-méthanol O-(phényl méthoxy-L-alaninyl) phosphate

Sel fumarate de (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentène-1-méthanol O-(phényl éthoxy-L-alaninyl) phosphate

Sel glutarate de (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentène-1-méthanol O-(phényl éthoxy-L-alaninyl) phophate

Sel D-tartrate de (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentène-1-méthanol O-(phényl éthoxy-L-alaninyl) phosphate

Diastéréoisomères de (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentène-1-méthanol O-(phényl méthoxy-L-alaninyl) phophate

Sel de (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentène-1-méthanol O-(phényl N-méthylamino-L-alaninyl) phosphate sodique

Sel de (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentène-1-méthanol O-(phényl N-cyclopropylamino-L-alaninyl) phosphate sodique

Sel de (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentène-1-méthanol O-(phényl N,N-diméthylamino-L-alaninyl) phosphate sodique

Sel de (1S,4R)-4-(2-amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopentène-1-méthanol O-(L-alaninyl) phosphate disodique

11. L'utilisation d'un composé suivant n'importe laquelle des revendications 1 à 3, la revendication 10 ou n'importe laquelle des revendications 5 à 9 comme il dépend de n'importe laquelle des revendications 1 à 3 dans la fabrication d'un médicament pour le traitement ou la prophylaxie d'une infection virale.

12. L'utilisation d'un composé suivant la revendication 11 où l'infection virale comprend le VIH.

13. L'utilisation d'un composé suivant la revendication 11 où l'infection virale comprend le VHB.

14. Un composé suivant n'importe laquelle des revendications 1 à 3, la revendication 10 ou n'importe laquelle des revendications 5 à 9 comme il dépend de n'importe laquelle des revendications 1 à 3 destiné à l'usage dans une méthode de traitement, de prophylaxie ou de diagnostic.

15. Un composé suivant la revendication 14 où la méthode comprend une méthode de prophylaxie ou de traitement d'une infection virale comprenant l'administration à un patient qui a besoin de ce traitement d'une dose efficace du composé.

16. Un composé suivant la revendication 15 où l'infection virale est le VIH.

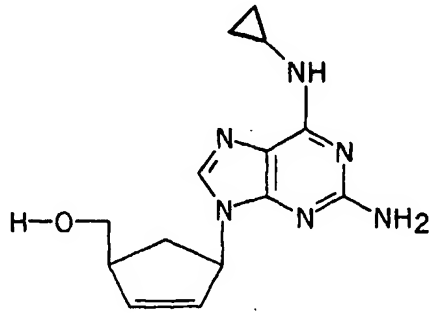
17. Un composé suivant la revendication 15 où l'infection virale est le VHB.

18. Un composé suivant n'importe laquelle des revendications 14 à 17 où la méthode comprend l'administration par voie orale à un patient d'une dose efficace de composé.

19. Une composition pharmaceutique comprenant un composé suivant n'importe laquelle des revendications 1 à 3, la revendication 10 ou n'importe laquelle des revendications 5 à 9 comme il dépend de n'importe laquelle des revendications 1 à 3 en association avec un excipient pharmaceutiquement acceptable.

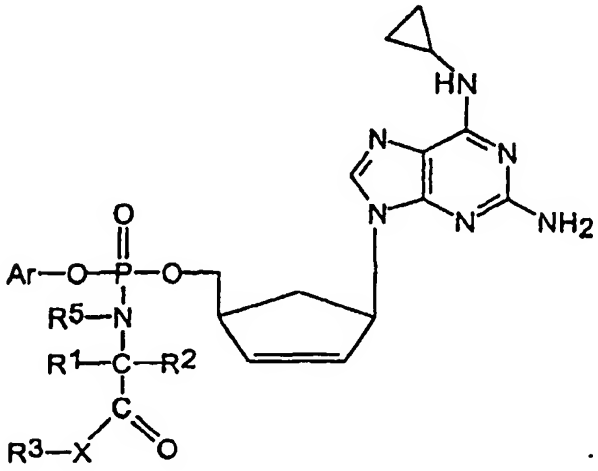
20. Une composition suivant la revendication 19 sous une forme destinée à la voie orale.

21. Un procédé pour la préparation d'un composé suivant n'importe laquelle des revendications 1 à 3, la revendication 10 ou n'importe laquelle des revendications 5 à 9 comme il dépend de n'importe laquelle des revendications 1 à 3 qui comprend la mise en réaction d'un composé qui a pour formule



Patentansprüche

1. Verbindung der Formel (I):



in der

Ar eine Arylgruppe ist;

R^1 und R^2 jeweils unabhängig aus der Gruppe gewählt werden, die H, Alkylund Arylgruppen umfasst;

X aus der Gruppe gewählt ist, die O, NH, NR^4 und S umfaßt, wobei R^4 aus der Gruppe gewählt ist, die Alkyl und Aryl umfaßt;

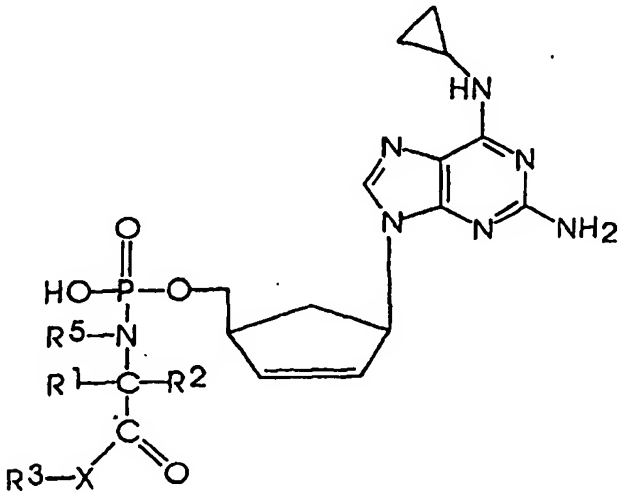
R^5 aus der Gruppe gewählt ist, die H, Alkyl- und Arylgruppen umfaßt, wobei, wenn R^1 und R^5 jeweils Alkyl sind, sie unter Bildung eines 5- oder 6-gliedrigen Ringes verknüpft sein können;

und R^3 aus der Gruppe gewählt ist, die H, Alkyl-, Aryl-, hetrocyclische und polycyclische Gruppen umfaßt; oder ein pharmazeutisch annehmbares Derivat oder Metabolit davon.

2. Verbindung gemäß Anspruch 1, wobei Ar Phenyl oder substituiertes Phenyl ist.

3. Verbindung gemäß einem der Ansprüche 1 bis 2, wobei R^3 aus der Gruppe gewählt ist, die $-CH_3$, $-C_2H_5$ und $-CH_2Ph$ umfaßt.

4. Verbindung der Formel (II):



in der R^1, R^2, R^3, R^5 und X die in Anspruch 1 zugewiesenen Bedeutungen besitzen.

5. Verbindung gemäß einem der Ansprüche 1 bis 4, in der R^1 und R^2 gleich oder unterschiedlich sind und H, $-CH_3$ oder $-CH_2CH_3$ sind.

6. Verbindung gemäß einem der Ansprüche 1 bis 4, in der R^1 H ist und R^2 $-CH_3$, $-CH_2CH_3$ oder $-CH_2$-Ph ist.

7. Verbindung gemäß einem der Ansprüche 1 bis 6, in der das C-Atom, welches R^1 und R^2 trägt, chiral ist.

8. Verbindung gemäß einem der Ansprüche 1 bis 6, in der die Verbindung L-Chiralität in Bezug auf das C-Atom, welches R^1 und R^2 trägt, besitzt.

9. Verbindung gemäß einem der Ansprüche 1 bis 8, in der X O ist.

10. Verbindung, gewählt aus:

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylmethoxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[L-alaninyl]phosphat-diammoniumsalz

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylbenzyloxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylmethoxy-D-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylmethoxy-α,α-dimethylglycinyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylmethoxy-L-phenylalaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylethoxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylmethoxyglycinyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenyl-L-aspartyldimethylester]phosphat

(1S, 4R)-4-(2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[4-chlorphenylmethoxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenyltertbutyloxy-L-alaninyl)phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenyl-n-propoxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenyl-n-butyloxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenyl-i-propoxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[(p-(2",2"-dimethoxypropionsäuremethylester)phenyl)methoxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenyl(2-methylpropyl)oxy-L-alaninyl]phosphat

(1S,4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenyl-(2,2-dimethylpropyl)oxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenyl-3-methylbutyloxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenyl-3-pentyloxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylmethoxy-L-valinyl] phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenyl-3,3-dimethyl-1-butyloxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenyl-n-pentyloxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylcyclohexylo-

xy-L-alaninyl]phosphat

(1S,4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylcyclohexanmethoxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylmethoxy-3-cyclohexan-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[4-bromphenylmethoxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenyldiethoxy-L-aspartyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylmethoxy-L-methionyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylmethoxy-L-leucinyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylmethoxy-L-prolinyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cycloproylamino)-9H-purin-9-yl]-2-cyclopenten-1-methylen-[phenyldibenzyloxy-L-aspartinyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenyl-4-methyl-1-pentyloxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylcyclopentylmethoxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[4-fluorphenylmethoxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[4-iodphenylmethoxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenyldimethoxy-L-glutamyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylmethoxy-L-tryptophanyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylmethoxy-L-isoleucinyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-Methanol-O-[phenylcycloheptanyloxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-Methanol-O-[phenylcyclobutylmethoxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-Methanol-O-[phenylcyclopropylmethoxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-Methanol-O-[phenylcyclobutyloxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylcyclopentyloxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylphenethoxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenyl-3-phenyl-1-propoxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenyl-4-phenyl-1-butoxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenyl-2-cyclohexyl-1-ethoxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenyl-3-cyclohexyl-1-propoxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenyl-4-cyclohexyl-1-butoxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylmethoxy-α-ethyl-L-glycinyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylmethoxy-α-phenyl(RS)glycinyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylmethoxy-α-propyl-L-glycinyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylmethoxy-α-butyl-RS-glycinyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[p-phenoxyphenylmethoxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[p-phenylphenyl methoxy-L-alaninyl)]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[4-hydroxyacetophenonmethoxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[4-butylphenylmethoxy-L-alaninyl]phosphat

(1 S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[p-methoxyphenylmethoxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[p-propoxyphenylmethoxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylmethoxy-α,α-cyclopentylglycinyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylmethoxy-α,α-cyclohexylglycinyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[phenylmethoxy-α,α-

cylopropylglycinyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[p-(methoxycarbonyl) phenylmethoxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[p-(trifluormethylthio) phenylmethoxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[p-(2-methoxyvinyl) phenylmethoxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[p-(2-phenylcarbonyl-vinyl)phenylmethoxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[p-(2,2-dicyanovinyl) phenylmethoxy-L-alaninyl]phosphat

(1S, 4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopenten-1-methanol-O-[o-(carboxylatethyle-ster)phenylmethoxy-L-alaninyl]phosphat

(1S, 4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopenten-1-methanol-O-(phenylethoxy-L-alaninyl)phosphat-succinatsalz

(1S, 4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopenten-1-methanol-O-(phenylmethoxy-L-alaninyl)-phosphat-succinatsalz

(1S, 4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopenten-1-methanol-O-(phenylethoxy-L-alaninyl)phosphat-fumaratsalz

(1S, 4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopenten-1-methanol-O-(phenylethoxy-L-alaninyl)phosphat-glutaratsalz

(1S, 4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopenten-1-methanol-O-(phenylethoxy-L-alaninyl)phosphat-D-tartratsalz

(1S, 4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopenten-1-methanol-O-(phenylmethoxy-L-alaninyl)phophatdiastereoisomere

(1S, 4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopenten-1-methanol-O-(phenyl-N-methyl-amino-L-alaninyl)phosphat-natriumsalz

(1S, 4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopenten-1-methanol-O-(phenyl-N-cyclopro-pylamino-L-alaninyl)phosphat-natriumsalz

(1S, 4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopenten-1-methanol-O-(phenyl-N,N-dime-thylamino-L-alaninyl)phosphat-natriumsalz

(1S, 4R)-4-(2-Amino-6-cyclopropylamino-9(H)-purin-9-yl)-2-cyclopenten-1-methanol-O-(L-alaninyl)phos-phat-dinatriumsalz

11. Verwendung einer Verbindung gemäß einem der Ansprüche 1 bis 3, gemäß Anspruch 10 oder gemäß einem der Ansprüche 5 bis 9, welche von einem der Ansprüche 1 bis 3 abhängen, bei der Herstellung eines Medikamentes zur Behandlung oder Prophylaxe einer viralen Infektion.

12. Verwendung einer Verbindung gemäß Anspruch 11, bei der die virale Infektion HIV umfaßt.

13. Verwendung einer Verbindung gemäß Anspruch 11, bei der die virale Infektion HBV umfaßt.

14. Verbindung gemäß einem der Ansprüche 1 bis 3, gemäß Anspruch 10 oder gemäß einem der Ansprüche 5 bis 9, welche von einem der Ansprüche 1 bis 3 abhängen, zur Verwendung bei einem Verfahren zur Behandlung, Prophylaxe oder Diagnose.

15. Verbindung gemäß Anspruch 14, bei der das Verfahren ein Verfahren der Prophylaxe oder Behandlung einer viralen Infektion umfaßt, umfassend das Verabreichen einer wirksamen Dosis der Verbindung an einen eine solche Behandlung benötigenden Patienten.

16. Verbindung gemäß Anspruch 15, wobei die virale Infektion HIV ist.

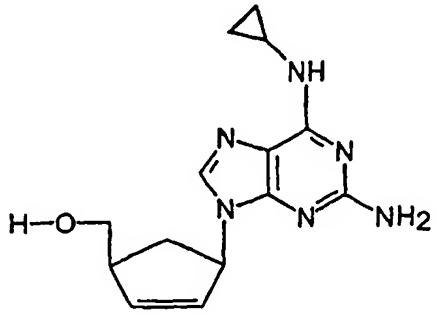
17. Verbindung gemäß Anspruch 15, wobei die virale Infektion HBV ist.

18. Verbindung gemäß mindestens einem der Ansprüche 14 bis 17, wobei das Verfahren das orale Verabreichen einer wirksamen Dosis der Verbindung an einen Patienten umfaßt.

19. Pharmazeutische Zusammensetzung, umfassend eine Verbindung gemäß einem der Ansprüche 1 bis 3, gemäß Anspruch 10 oder gemäß einem der Ansprüche 5 bis 9, welche von einem der Ansprüche 1 bis 3 abhängen, in Kombination mit einem pharmazeutisch annehmbaren Vehikel.

20. Zusammensetzung gemäß Anspruch 19 in einer Form zur oralen Verabreichung.

21. Verfahren zur Herstellung einer Verbindung gemäß einem der Ansprüche 1 bis 3, gemäß Anspruch 10 oder gemäß einem der Ansprüche 5 bis 9, welche von einem der Ansprüche 1 bis 3 abhängen, umfassend das Umsetzen einer Verbindung der Formel



mit einer Verbindung der Formel